16.1.1 Protocol and Protocol Amendments

18-ICH-001 Protocol Amendment 3, Final Protocol Version 4.0 (Ukraine), dated 19-Nov-2020

18-ICH-001 Protocol Amendment 2, Final Protocol Version 3.0, dated 28-Oct-2020

18-ICH-001 Protocol Amendment 2, Final Protocol Version 3.0 (Ukraine), dated 21-Nov-2019

18-ICH-001 Protocol Amendment 1, Final Protocol Version 2.0 (Ukraine), dated 21-Oct-2019

18-ICH-001 Protocol Amendment 1, Final Protocol Version 2.0, dated 10-Jul-2019

18-ICH-001 Protocol, Final Protocol Version 1.0, dated 28-Nov-2018

PROTOCOL/CLINICAL INVESTIGATION PLAN AMENDMENT

PRODUCT NAME/NUMBER:	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER:	18-ICH-001
IND NUMBER:	140538
NCT NUMBER:	NCT03738800
EUDRACT NUMBER:	2018-003272-12
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 90-Day, Safety, Efficacy, and Systemic Exposure Study followed by a 90-Day Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
PROTOCOL DATE:	Original: 28-Nov-2018
AMENDMENT 1 DATE:	Final v2.0, 21-Oct-2019
AMENDMENT 2 DATE:	Final v3.0 for Ukraine, 21-Nov-2019
AMENDMENT 3 DATE:	Final 4.0 for Ukraine, 19-Nov-2020
COORDINATING/PRINCIPAL INVESTIGATOR:	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine, PO Box 208059 333 Cedar Street New Haven, CT 06520, USA +1 203 789 1249
SPONSORED BY:	Mayne Pharma LLC 1240 Sugg Parkway Greenville, NC 27834, USA +1 984 242 1400
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive, Suite 150 Durham, NC 27709, USA +1 919 627 9100

This study will be performed in compliance with ICH Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the institutional review board or independent ethics committee, or as required by law. Persons to whom this information is disclosed should be informed that it is confidential and may not be further disclosed without the express permission of Mayne Pharma LLC.

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: 18-ICH-001

PROTOCOL TITLE: A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 90-Day, Safety, Efficacy, and Systemic Exposure Study followed by a 90-Day Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale

I, the undersigned, have read this protocol and confirm that to the best of my knowledge, it accurately describes the planned conduct of the study.

SIGNATURE	DATE:
DocuSigned by: Phoevos Hughes Signer Name: Phoevos Hughes Signing Reason: I approve this document Signing Time: 20-Nov-2020 | 06:28:06 PST ID: 2D1DCFCA65A8487B371307AF875E4CE Phoevos Hughes, JD Head of Medical and Clinical Affairs Mayne Pharma LLC	20-Nov-2020 | 06:28:08 PST
DocuSigned by: Marlis Sarkany Signer Name: Marlis Sarkany Signing Reason: I have reviewed this document Signing Time: 23-Nov-2020 | 03:54:26 EST ID: 116E1C8AEDC854ODC86688C1FD466E26F Marlis Sarkany, MD Senior Medical Director Premier Research	23-Nov-2020 | 03:54:30 EST
DocuSigned by: Valerie Smith Signer Name: Valerie Smith Signing Reason: I approve this document Signing Time: 20-Nov-2020 | 09:21:50 EST ID: 5[illegible]AA9FA446FC310D506 Valerie H. Smith Manager, Biostatistics Premier Research	20-Nov-2020 | 09:21:52 EST

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER	18-ICH-001
EUDRACT NUMBER	2018-003272-12
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 90-Day, Safety, and Efficacy, and Systemic Exposure Study followed by a 90-Day Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
INDICATION	Lamellar ichthyosis
OBJECTIVES	Primary: To compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in subjects with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 90 days of treatment. Secondary: • To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% body surface area (BSA) twice weekly. • To assess safety for up to 180 days of dosing with open-label trifarotene cream HE1 200 µg/g.
STUDY DESIGN	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Investigator's Global Assessment [IGA] where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe). Adults will be randomized in a double-blind fashion to 1 of 2 doses of trifarotene cream HE1 or vehicle and treated twice weekly for 90 days. Subjects who complete the randomized, Double-blind Period of the study will be eligible to enter a 90-day, Open-label Extension (OLE) in which additional PK, safety, and efficacy data will be collected. Subjects will be randomized into the first cohort of subjects (Cohort A) in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 90 days. After the initial 15 subjects complete at least 28 days of treatment, an independent data safety monitoring board (DSMB) will review aggregate safety and tolerability data (including PK and electrocardiogram [ECG] data). If no safety issues are identified, an additional group of approximately 105 subjects will be allowed to enroll in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 90 days in the same manner as subjects in Cohort A. All subjects (Cohort A and Cohort B) who complete the 90-day Double-blind Treatment Period will be eligible to enroll in the 12-week OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for up to 12 weeks. Upon signing informed consent and entering the Screening Period, a Washout Period of 90 days. Participants will stop using physical and medical treatments for LI, including

balneotherapy, as well as the following prohibited medications, as applicable. The following list applies to both prescription and over-the-counter medications:

a. Topical treatments

Medication	Washout
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	2 weeks

b. Systemic treatments

Medication	Washout
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones unless the dose is stable and thyroid-stimulating hormone (TSH) is normal, cytotoxics, bisphosphonates, selective estrogen receptor modulators (SERM), teriparatide, calcitonins, tetracyclines, quinolones, thiazides, long-term use of salicylates, heparin, theophylline, barbiturates, colchicines. Vitamin D analogs taken at stable dose for at least 30 days are allowed)	8 weeks
QT-prolonging drugs	5 half lives
CYP enzymatic inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (including, but not limited to the following: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives
Monoclonal antibodies	5 half lives

Before asking a subject to washout of their prescription and over-the-counter prohibited treatments, investigators should confirm the subject meets all study eligibility criteria except for LI severity (inclusion criterion #3). After completing the necessary washout period, subjects will return to the site to have their LI severity assessed and to complete study eligibility requirements.

During washout, subjects may continue their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard of care treatments in the electronic case report form (eCRF). If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit.

Subjects may shower, but not bathe or swim during the Screening Period.

Study drug will be packaged in 50-g tubes from which up to 36 g of IP may be dispensed per application, i.e., the maximum dose per application. Study staff will choose 1 tube from the kit dispensed to the subject at that visit, and apply the first dose of study drug to

	each subject in the clinic on Day 1 after Baseline measurements; they will weigh the study tube before and after application to determine the amount used. If the product will be applied at home by someone other than the study subject, it is recommended that this person assist with application at the first visit to learn how the IP is applied. The kit dispensed at Baseline must be weighed before the first tube is chosen for application by the study staff. Weight of the kits dispensed and returned by the subject during the study includes both tubes and cartons, but not leaflets, which need to be removed before weighing. The subject must be reminded to return the kits with tubes and cartons, whether used or not, when returning to the next visit. Thereafter, each subject will apply up to 36 g of study drug as for the first dose on up to 90% of BSA twice weekly, 3 to 4 days apart, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of product in a tube. Subjects will record the date and time of study treatment administration in the subject diary. The study protocol limits application of IP to 36 g maximum; no additional tubes can be given, whether during the randomization period or the OLE period. If the study staff and subject note that there is insufficient volume for full body application, the subject should apply trifarotene cream sparingly twice weekly to the most affected areas, and always to the same skin areas. Study cream should be very sparingly applied. Trifarotene cream 100 or 200 µg/g is a highly potent topical retinoid, and it is not necessary to apply much for efficacy; application of more will increase the risk of irritation and systemic penetration. Local tolerability may differ in subjects with LI compared to healthy subjects, as their skin is drier and may be more sensitive. Local tolerability will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45 in the Double-blind Period; at Day 97 and 134 in the OLE) to assess safety; an unscheduled clinic visit may be performed, if necessary. If the treatment causes application site reactions, the frequency of application will be reduced or interrupted only on the area of concern, as indicated herein. During all clinic visits, the investigator will assess local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]) for each body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed: - If a score of 2 (moderate) is recorded for any of the local tolerability assessment scales (stinging/burning, pruritus, or erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas. - If a score of 3 (severe) is recorded for any of the local tolerability assessment scale (stinging/burning, pruritus, or erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., “drug holiday”). Continue to treat all other areas twice weekly provided the score is <2 on those areas. Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and adverse events (AEs). Any changes in dosing must be documented in the subject diary and the electronic case report form. All subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]) and any AEs, including application site reactions and concomitant medications used. Subjects will also be advised on permitted emollient(s) use on nontreatment days during the study; use of

	emollient(s) and/or sunscreen(s) on study drug treatment days within 4 hours before or after study drug application is prohibited.
	
	At all sites with photographic capability, photographs will be taken as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional photographic informed consent form (ICF).
	
	Samples for pharmacokinetic (PK) analysis will be drawn from all subjects at Baseline and at each clinic visit. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained on the skin after the last application. Subjects should not apply IP on visit days until after the visit.
	
	In addition, a PK substudy will be conducted on Days 1 and 30 at sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 30 subjects. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for these subjects at each of the other clinic visits. For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30.
	
	Subjects who complete the Double-blind Treatment Period will have the option to continue into the OLE to assess safety for an additional 90 days with trifarotene cream HE1 200 µg/g twice weekly, on up to 90% of BSA, sparing the scalp, inguinal, and axillary areas. During the study, subjects with heavy facial hair should not apply IP to hair-bearing areas. During the OLE, subjects will return to the site at Days 104, 120, 150, 180, and 194 for safety, tolerability, and efficacy assessments. Blood samples will be drawn for clinical laboratory safety tests and PK at Days 120 and 180. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 97 and Day 134) to assess safety; an unscheduled clinic visit may be performed, if necessary.
	
	The coronavirus disease 2019 (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted in order to control the spread of the disease. It is recommended that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19.
	
	Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 (Double-blind Period; Table 2-1), Visits 7-11 (OLE Period; Table 2-2) and unscheduled visits may be conducted remotely. Screening and Baseline Visits must be performed on site only. These visits must be postponed or scheduled for when onsite visits can be safely conducted. The following assessments may occur remotely:
	
	• Safety Assessments
	  o Concomitant medications and concomitant therapies
	  o Adverse Events and related information reported by the patient in the diary
	  o General health status of the subject
	• Tolerability Assessments
	• Pregnancy Tests: Urine pregnancy tests along with the instructions on proper use will be sent to the subject's home for women of childbearing potential (WOCBP). Study staff will instruct patient to perform the urine pregnancy at the applicable remote visit.

	• Study Medication Supply: As necessary and according to applicable local regulations, study medication will be sent to subjects. • DLQI and EQ-5D Questionnaires: Quality of Life questionnaires should be completed on the day of the remote visit and prior to applying treatment (if the remote visit falls on a treatment day). Questionnaires may be sent to subjects electronically or via postal service, and completed questionnaires may be returned to the site in the same manner. If subjects are unable to send completed questionnaires to the site, investigators should ask and record the subject's responses during the remote visit. • Subject Diary: Subject diaries may be sent to subjects electronically or via postal service. Completed diaries may be returned to the site in the same manner.
PLANNED NUMBER OF SUBJECTS	Approximately 120 total subjects; 15 subjects in Cohort A and 105 subjects in Cohort B.
STUDY ENTRY CRITERIA	Inclusion criteria: 1. Subject is ≥18 years old. 2. Subject has known diagnosis of LI. 3. Subject has moderate to severe (IGA 3-4) LI on the IGA of LI severity. 4. Subject has signed an ICF at Screening before any investigational procedures. 5. Subject who is participating in photography has signed a photography ICF. 6. Subject who is participating in the optional PK substudy has signed a PK ICF. 7. Subject is not of childbearing potential, who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason), or has documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry. OR Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception: • bilateral tubal ligation • combined oral contraceptives (estrogens and progesterone), vaginal ring, or implanted or injectable hormonal contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation • intrauterine device (IUD) inserted at least 1 month before Baseline OR Agrees to abstain from heterosexual intercourse during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. AND

	Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application. 8. Women of childbearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine). 9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent. 10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin). Exclusion criteria: 1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization, including syndromic ichthyoses. 2. Subject has current moderate or severe stinging/burning at Screening. 3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments. 4. Subject with fasting triglycerides >200 mg/dL or >2.25 mmol/L and/or total cholesterol >250 mg/dL or >6.5 mmol/L. Subjects whose triglycerides and/or total cholesterol are within normal limits with a stable dose of lipid-lowering agents for at least 6 months may be included. 5. Subject was previously treated with trifarotene/CD5789 in an acne or ichthyosis study. 6. Subject has any other significant concomitant disease, or poorly controlled medical condition other than LI that in the investigator's opinion may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis). Subjects with hypothyroidism who are on a stable dose of thyroid hormone replacement therapy and whose TSH is normal may be included. 8. Subject is being treated for major depression disorder and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts. 9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening. 10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal (ULN) defined by the laboratory b. Total bilirubin >1.25 × ULN at Screening. Subjects with known Gilbert's syndrome may be included with total bilirubin >1.25 × ULN c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women d. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L 11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 12. Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment.

	13. Subject has a history of long QT syndrome or has clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, or QTcF interval >450 ms. 14. Subject has a known allergy or sensitivity to any of the components of the investigational products. 15. Subject has been exposed to excessive ultraviolet (UV) radiations on the treated zones within 1 month before Baseline visit or is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.). 16. Subject is inherently sensitive to sunlight. 17. Subject is unable or unwilling to stop use of topical or systemic retinoids. 18. Subject is presumed to be abusing drugs or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms. 19. Subject is participating in another interventional clinical trial. 20. Subject is institutionalized. 21. Subject is in any way related to the sponsor, investigator, or site personnel.
INVESTIGATIONAL PRODUCT	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: Up to 36 g per dose of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Extension dose, route, frequency: Up to 36 g per dose of 200 µg/g applied topically twice weekly on up to 90% BSA
REFERENCE PRODUCT	Name: Vehicle cream Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) applied topically twice weekly on up to 90% BSA
TREATMENT REGIMENS	Topical application twice weekly to all affected skin except the scalp, axillae, and inguinal area.
COORDINATING/ PRINCIPAL INVESTIGATOR	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine New Haven, CT 06520, USA
PLANNED STUDY SITES	Approximately 40 sites across North America, Europe, Israel, and Australia

CRITERIA FOR EVALUATION	Primary efficacy endpoint: The proportion of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear on treated areas and at least a 2-grade change from Baseline at Day 90/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA full body scale.
	
	Secondary endpoints:
	
	– The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Day 90:
	  – 5-point Visual Index for Ichthyosis Severity (VIIS) for scaling (overall 16 points for scaling, i.e., 0-4 points for 4 body areas: chest/abdomen, back, arms, and legs)
	  – Individual score for roughness (Scale: 0–4)
	  – Palm/sole Assessment (Scale: 0–4)
	  – Quality of life per Dermatology Life Quality Index (DLQI)
	– The difference in proportion of subjects with presence of fissures on palms/soles (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) at Day 90 between the active trifarotene cream HE1 and vehicle groups
	
	Exploratory endpoints:
	
	– The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90
	– The difference in quality of life per EQ-5D-5L score between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90
	
	Safety endpoints:
	
	– Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs
	– Local tolerability (stinging/burning, pruritus, or erythema on: 0-3 scales [none, mild, moderate, severe]) for each body area (chest/abdomen, back, legs, arms, and face/neck)
	
	Pharmacokinetic endpoints: Plasma concentrations of CD5789 and its major metabolites will be measured.

STATISTICAL METHODS	Analysis Populations: The following are planned for the Double-blind Period of the study: The Safety population will be the primary population for analyses of safety and tolerability and will comprise all subjects who are randomized to treatment and receive at least 1 application of study drug. The intent-to-treat (ITT) population will comprise all randomized subjects. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The modified intent-to-treat (mITT) population comprises all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The per protocol (PP) population will be defined prior to database lock and will comprise subjects in the mITT population who met all inclusion criteria and no exclusion criteria,

	were compliant with study drug application, and who had no significant protocol deviations. The PK population includes all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. The PK population will be used to summarize all PK endpoints. The following populations are planned for the OLE of this study: The OLE Safety population: all subjects who complete the 90-day Double-blind Treatment Period and receive at least 1 application of study drug in the OLE. OLE ITT population: all subjects who complete the 90-day Double-blind Period and who sign the OLE informed consent. The OLE mITT population: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6. The OLE PP population: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study. Subject Characteristics and Disposition: Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and baseline characteristics for all enrolled subjects. Medical history, physical examination findings, and vital sign measurements for all randomized subjects will be presented in listings. Efficacy Analyses: The number and proportion of subjects in each treatment group with successful resolution of LI by Day 90/EOT in the Double-blind Period will be presented. The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream groups, 95% CIs for the differences, and P-values for the differences in treatment will also be presented. The IGA scores as well as secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Day 180 (end of OLE treatment period). Change from Baseline through Day 90 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from Baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and Baseline score value as a covariate. Frequencies of results and 95% confidence intervals will also be reported, and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test. For subjects who report having fissures, the number of fissures and pain related to fissures will also be presented on a scale of 0-3 (none, mild, moderate, severe). Clinical Pharmacology Analyses: Noncompartmental PK analysis will be performed for the PK subset of subjects, as data permit. Plasma concentrations of CD5789 and its major metabolites will be measured and will be listed by subject. Safety Analyses: Safety and tolerability will be assessed based on the incidence of reported TEAEs, and SAEs, including relationship to study drug and severity, as well as physical examination findings, vital sign measurements (supine systolic blood pressure [SBP] and diastolic blood pressure [DBP] and pulse), clinical laboratory results (hematology, including serum aminotransferases and serum lipids, coagulation, clinical chemistry, and urinalysis) and 12-lead ECGs. Descriptive statistics for observed values and change from Baseline will be calculated at each visit within each study period and by treatment group within cohort.

SAMPLE SIZE DETERMINATION	The first cohort of 15 subjects is a reasonable sample size to assess safety and tolerability before enrolling additional subjects in Cohort B. Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively. This study is not powered to detect a difference between the 2 active arms.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study periods for each subject will be as follows: 1. Screening: Up to 97 days. Before asking a subject to enter washout, investigators should confirm the subject meets study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined. 2. Double-blind study drug application: Twice weekly for 90 days. 3. Optional Open-label Extension: Twice weekly for 90 days. 4. Follow-up: 14 days after last study drug application. The maximum treatment duration for each subject is approximately 90 days for subjects who choose not to continue into the OLE, and 180 days for those who choose to continue. The maximum treatment duration for each subject is 291 days.

2.2. Schedule of Events

Table 2-1: Schedule of Events for Double-blind Period

	Screening (-97 days to -1 day) Washout up to 90 days[a]	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[b,c] ± 7 days (ET)
Visit	**1**	**2**		**3[d]**	**4[d]**		**5[d]**	**6[d]**
Written informed consent	X							X[a]
Assign screening number	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical history	X							
Physical examination	X	X[e]						X[e]
Vital signs (blood pressure and pulse)	X	X		X	X		X	X
Height, weight, and BMI	X							X[b]
IGA assessment[f]	X	X		X	X		X	X
VIIS[g] assessment	X	X		X	X		X	X
Roughness assessment[h]	X	X		X	X		X	X
Palm/sole assessment	X	X		X	X		X	X
Palm/sole fissuring assessment[i]	X	X		X	X		X	X
Ectropion score	X	X		X	X		X	X
Photographs[j]		X			X			X
Quality of life per Dermatology Life Quality Index (DLQI)		X		X	X		X	X
EQ-5D Quality of Life Questionnaire		X		X	X		X	X

	Screening (-97 days to -1 day) Washout up to 90 days[a]	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[b,c] ± 7 days (ET)
Visit	**1**	**2**		**3[d]**	**4[d]**		**5[d]**	**6[d]**
12-lead ECG[k]	X	X			X			X
Clinical laboratory tests (hematology, chemistry, urinalysis)[l]	X	X			X			X
Serology (hepatitis B surface antigen, hepatitis C)	X							
Coagulation panel		X			X			X
Pregnancy test for female subjects (serum at Screening; urine subsequently)	X	X			X		X	X
Randomization via IWRS		X						
PK blood sample collection[m]		X		X	X		X	X
Initial study drug application by clinic staff and measurement[n]		X						
Application instructions, advice on emollient and sunscreen use		X	X	X	X	X	X	X
Dispense study drug and diaries[o]		X		X	X		X	(X)[o]
Concomitant medications	X	X	X	X	X	X	X	X
Tolerability assessment		X		X	X		X	X
Adverse events (and review diaries)		X	X	X	X	X	X	X
Collect all used/unused study drug[p]				X	X		X	X
Provide information about OLE option					X	X	X	X

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; HEENT = head, eyes, ears, nose, throat; ICF = informed consent form; IGA = Investigator's Global

Assessment; IWRS = interactive web response system; OLE = open-label extension; PK = pharmacokinetic; WOCBP = women of childbearing potential; VIIS = Visual Index for Ichthyosis Severity

a. Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and begin to washout prohibited topical and systemic treatments with designated washout periods, as applicable. Before asking a subject to enter washout, investigators should confirm the subject meets study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined. During washout, subjects may continue their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard of care treatments in the electronic case report form (eCRF). If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower, but not bathe or swim during the Screening Period.
b. Day 90 procedures should be conducted for subjects who terminate the study early. If a subject discontinues IP, but continues to attend clinic visits, Day 90 will occur as scheduled. Day 90 will be the first visit of the OLE for subjects who choose to continue. Subjects who decide to continue into the OLE will have the following additional procedures: 1) sign informed consent; 2) will be weighed; 3) will be instructed on study drug application; 4) will be given new diaries, and 5) will be provided with study drug.
c. A Follow-up telephone call will be made within 14 days after Day 90 to subjects who choose not to continue into the OLE to assess any ongoing adverse events.
d. Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 and unscheduled visits may be conducted remotely. Screening and Baseline Visits must be performed onsite only, and must be postponed or scheduled for when onsite visits can be safely conducted.
e. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
f. IGA: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe.
g. VIIS scale for each body area: chest/abdomen, back, legs, and arms, for a possible overall score = 16.
h. Roughness (0-4 scale);
i. Palm/sole fissuring assessment: present/absent/number/pain (0-3 scale).
j. Photography will be performed at sites with the capability for subjects who sign a photographic ICF. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check.
k. ECG to be conducted at Screening, Baseline, Day 30, and Day 90 for all subjects. Subjects in the PK substudy will also have postdose ECGs at each serial blood draw on Day 1 and Day 30.
l. Subjects must be fasting (i.e., at least 8 hours) for clinical laboratory tests, but not for PK blood draws.
m. Samples for PK will be drawn from all subjects at Baseline and at each clinic visit. At selected sites among subjects who consent to participate in the PK substudy, samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1. On Day 30, IP will be applied in the clinic for PK substudy subjects, and PK samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose. Trough levels will be drawn when the subjects are in the clinic for other study visits (i.e., Day 14, Day 60, and Day 90). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.
n. Study staff will apply initial dose of study drug in the clinic after Baseline measurements, and the amount of study drug used will be measured (i.e., 36-g tube will be measured before and after application to determine amount used).
o. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug kits (tubes and box, but not leaflets) before dispensing; subjects must record days/times of study drug application in the diaries and any areas of skin not treated, e.g., due to local reactions). Dispense enough additional study drug until next visit (except at Day 90, unless subject consents to continue into OLE).

p. Confirm study drug compliance by weighing the study kits (tubes and boxes, but not leaflets) and reviewing diary.

Table 2-2: Schedule of Events for Open-label Extension

	Open-label Treatment Period[a]						Follow-up
	Telephone Visit (Day 97)	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7[a]**	**8[a]**		**9[a]**	**10[a]**	**11[a]**
Informed consent[b]							
Physical examination[c]						X	X
Vital signs (blood pressure and pulse)		X	X	X	X	X	X
Record IGA[d]		X	X		X	X	X
VIIS[e] assessment		X	X		X	X	X
Roughness assessment[f]		X	X		X	X	X
Palm/sole assessment		X	X		X	X	X
Palm/sole fissuring assessment		X	X		X	X	X
Ectropion score		X	X		X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)[g]			X			X	
Pregnancy test for female subjects (urine)			X		X	X	X
Coagulation panel			X			X	
12-lead ECG			X			X	
PK blood sample collection[h]			X			X	
Application instructions, advice on emollient and sunscreen use	X	X	X	X			
Dispense study drug and diaries[j]		X	X		X		

	Open-label Treatment Period[a]						Follow-up
	Telephone Visit (Day 97)	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7[a]**	**8[a]**		**9[a]**	**10[a]**	**11[a]**
Concomitant medications	X	X	X	X	X	X	X
Tolerability assessment		X	X		X	X	
Adverse events (and review diaries)	X	X	X	X	X	X	X
Collect all used/unused study drug[k]		X	X		X	X	

Abbreviations: ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears, nose, throat; ICF = informed consent form; IGA = Investigator's Global Assessment; PK = pharmacokinetic; OLE = open-label extension; VIIS = Visual Index for Ichthyosis Severity; WOCBP = women of childbearing potential

a. Although it is preferable to conduct all necessary study assessments in person (on -site visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 7-11 and unscheduled visits may be conducted remotely.
b. Subjects will sign the OLE ICF at the Double-blind Day 90 Visit. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing and PK from Day 90 will be carried over for the OLE and will not be repeated.
c. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
d. IGA: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe
e. VIIS scale for each body area: chest/abdomen, back, legs, and arms, for a possible overall score = 16.
f. Roughness (0-4 scale); fissuring assessment on palms/soles: present/absent/number/pain (0-3 scale).
g. Subjects must be fasting (at least 8 hours) for clinical chemistry testing, but not for PK only blood draws.
h. Samples for PK will be drawn from all subjects at Day 120 and Day 180. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.
i. All subjects in the OLE will receive trifarotene 200 µg/g. Study drug provided in 50-g tubes (maximum single application is 36 g). Weigh study medication kits (tubes and box, but not leaflets). Dispense enough additional study drug until the next visit (except at Day 180).
j. Subjects must record days/times of study drug application in the diaries and any areas of skin not treated (e.g., due to local reactions).
k. Confirm study drug compliance by measuring weighing the study kits (tubes and boxes, but not leaflets) dispensed and returned and reviewing diary.

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

3.2. List of In-Text Figures

REASONS FOR AMENDMENT

Protocol Amendment 3 is a major amendment that addresses feedback from the Regulatory Agencies, Competent Authorities, Central Ethics Committees, and investigators. The following changes were made:

1. Changed all times defined as “weeks” to “days” throughout
2. Added new Section (Section 10.4) and Appendix B for procedural adjustments due to COVID-19.
3. Updated Phoevos Hughes’ title.
4. Changed name and title of Statistician.
5. Clarified that Cohort A may continue enrolling subjects until the DSMB considers it safe to open recruitment in Cohort B.
6. Clarified that washout periods apply to both prescription and over-the-counter medications.
7. Clarified that subjects receiving stable thyroid hormone medications with normal thyroid-stimulating hormone levels may be eligible for enrollment.
8. Clarified that subjects taking stable oral doses of Vitamin D analogs for at least 1 month at Screening may be eligible for enrollment.
9. Clarified and made consistent the definition of standard of care for visible skin (face and scalp) and of extremities (palms and soles).
10. Deleted “fixed dose” or “same amount” of IP throughout.
11. Aligned power calculation and parameter assumptions with the new primary endpoint.
12. Added optional photography evaluation of scoring by a central reader who is not a study investigator as a quality check.
13. Clarified that local tolerability comprises any stinging/burning, pruritus, or erythema and that each should be assessed on a 0-3 point scale.
14. As requested by the ethics committee in Australia, clarified definition of women of childbearing potential and clarified that a hormonal vaginal ring or an IUD inserted at least 30 days before Baseline is an acceptable second form of contraception (i.e., IUD does not have to be hormonal).
15. Revised Exclusion Criterion #4 to define exclusionary levels of triglycerides and total cholesterol, and to allow subjects with normal levels of triglycerides and/or total cholesterol on stable doses of lipid-lowering agents for at least 6 months to be eligible for inclusion.
16. Revised Exclusion Criterion #10b with regard to exclusionary total bilirubin levels at Screening and defined acceptable levels for subjects with known Gilbert’s Syndrome (>1.25 × upper limit of normal [ULN]).
17. Clarified Exclusion Criterion #13 to remove specific PR and QRS levels and heart rates.
18. Extended the Screening Period to allow for up to 90 days of washout, and clarified that all Screening procedures, with the exception of LI assessment, should be performed before a subject begins the Washout Period. The subject will return after completing the washout period for LI assessment and to confirm eligibility.

19. Revised Figure 7-1 and Figure 7-2 to correct typos and to change weeks to days.
20. Revised Table 2-1 and Table 2-2 to correct timing and omissions.
21. Clarified the intervals between IP applications and added a table to illustrate a twice-weekly schedule.
22. Removed location for Catalent Pharma Solutions.
23. Clarified that subjects who participate in the PK substudy should have their Day 30 Visit scheduled on a treatment day, and that investigators should contact the medical monitor if that is not possible.
24. Added a coagulation panel to the study procedures.
25. Added the composition and qualifications of the DSMB.

SUMMARY OF AMENDED SECTIONS

Section	Previous Text	Revision	Rationale
Title throughout document	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 12-week Safety, Efficacy, and Systemic Exposure Study followed by a 12-week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, **90-Day**, Safety, Efficacy, and Systemic Exposure Study followed by a **90-Day** Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale	To be more precise about time intervals
Document	"Weeks"	Changed all to days	To be more precise about time intervals
Synopsis and Section 7	Approximately **15 subjects** will be randomized into the first cohort of subjects (Cohort A) in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g, trifarotene cream HE 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks.	Subjects will be randomized into the first cohort of subjects (Cohort A) in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 90 days	To clarify that Cohort A may enroll more than 15 subjects total.
Synopsis and Section 9.8	Upon signing informed consent and entering the Screening Period, subjects may begin washout, during which they will stop using physical and medical treatments for LI, including balneotherapy, and the following prohibited medications, as applicable.	Upon signing informed consent and entering the Screening Period, subjects may begin **a Washout Period of up to 90 days**. Participants will stop using physical and medical treatments for LI, including balneotherapy, **as well as** the following prohibited medications, as applicable. Added: the following list applies to both prescription and over-the-counter medications:	To clarify
Synopsis and Section 9.8	Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines. (except Vitamin D analogs taken at stable dose since at least 1 month.	Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones **unless the dose is stable and thyroid-stimulating hormone (TSH) is normal**, cytotoxics, bisphosphonates, **selective estrogen receptor modulators (SERM), teriparatide,** calcitonins, tetracyclines, quinolones, thiazides, **long-term use of** salicylates, heparin, theophylline, barbiturates, colchicines. Vitamin D analogs	Added prohibited medications and clarified which medication interfering with bone activity is acceptable.

		taken at stable dose **for at least 30 days are allowed.**	
	Enzyme inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	**CYP** enzyme inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	To clarify
	CYP2C9 and 2C8 inhibitors (not all inclusive, gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	CYP2C9 and 2C8 inhibitors **(including, but not limited to the following**: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	
	Monoclonal antibody treatment (e.g., anti IL17	Monoclonal **antibodies**	
Synopsis, Table 2-1 footnote a, and Sections 7.1, 9.8, and 10.2.1.1 and 10.2.1.1.1	During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hand/feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower, but not bathe or swim, during the Screening Period. After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements. Subjects may shower, but not bathe or swim. After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.	Added: Before asking a subject to enter washout of their prescription and over-the-counter prohibited treatments, investigators should confirm the subject meets all study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and to complete study eligibility requirements During washout, subjects may continue **their standard of care** of visible skin (face and scalp) for cosmetic reasons and of extremities (**palms/soles**) to avoid functional consequences on walking or moving their fingers. **In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard-of-care treatments in the electronic case report form (eCRF). If the standard**	To ensure subjects do not have to repeat screening assessments after washout. To better define standard of care and prevent confusion.

		of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower, but not bathe or swim.	
Synopsis and Section 7.1	Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied.	Study staff will **choose 1 tube from the kit dispensed to the subject at that visit, and apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements; they will weigh the study tube before and after application to determine the amount used.** Added: The kit dispensed at baseline must be weighed before the first tube is chosen for application by the study staff. Weight of the kits dispensed and returned by the subject during the study includes both tubes and cartons, but not leaflets, which need to be removed before weighing. The subject must be reminded to return the kits with tubes and cartons, whether used or not, when returning to the next visit.	To clarify how amount of IP applied is determined To ensure kits are weighed appropriately before dispensing to the subject and upon return
Synopsis	Thereafter, each subject will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas.	Thereafter, each subject will apply study drug on up to 90% of BSA twice weekly **3 to 4 days apart,** sparing the scalp, inguinal, and axillary areas. Added: **Subjects with heavy facial hair should not apply IP to hair-bearing areas**. Added: The study protocol limits application of IP to 36 g maximum; no additional tubes can be given, whether during the randomization period or the OLE period. If the study staff and subject note that there is insufficient volume for full body application, the subject should apply trifarotene cream sparingly twice weekly to the most affected areas, and always to the same skin areas. Study cream should be very	Removed fixed amount/same amount because of the natural variations in the extent and severity of LI. To not apply IP to hair-bearing areas for the first 90 days. To address questions about the amount of cream to apply when a single tube does not seem to be enough

		sparingly applied. Trifarotene cream 100 or 200 µg/g, is a highly potent topical retinoid and it is not necessary to apply much for efficacy; application of more will increase the risk of irritation and systemic penetration.	
Synopsis, Sections 7.1, 9.4, and 13.1.6.1	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for stinging/burning, pruritus, erythema) for each body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed: - If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas. - If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas.	During all clinic visits, the investigator will assess local tolerability (**stinging/burning, pruritus, or erythema on 0-3 scales** [none, mild, moderate, severe]) for each body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed: - If a score of 2 (moderate) is recorded **for any of the** local tolerability assessment scale**s** (stinging/burning, pruritus **or** erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas. - If a score of 3 (severe) is recorded **for any of the** local tolerability assessment scale**s** (stinging/burning, pruritus **or** erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas.	To clarify that any of the 3 local tolerability conditions may warrant modification of dosing frequency
Synopsis		Added: The coronavirus disease 2019 (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted in order to control the spread of the disease. It is recommended	

		that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19. Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19 -related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 (Double –blind Period; Table 2-1), Visits 7-11 (OLE Period; Table 2-2) and unscheduled visits may be conducted remotely. Screening and Baseline Visits must be performed on site only. These visits must be postponed or scheduled for when onsite visits can be safely conducted. The following assessments may occur remotely: • Safety Assessments o Concomitant medications and concomitant therapies. o Adverse Events and related information reported by the patient in the diary o General health status of the patient • Tolerability Assessments • Pregnancy Tests: Urine pregnancy tests along with the instructions on proper use will be sent to the subject's home for women of childbearing potential (WOCBP). Study staff will instruct patient to perform the urine pregnancy at the applicable remote visit. • Study Medication Supply: As necessary and according to applicable local regulations, study	

		medication will be sent to subjects. • DLQI and EQ-5D Questionnaires: Quality of Life questionnaires should be completed on the day of the remote visit and prior to applying treatment (if the remote visit falls on a treatment day). Questionnaires may be sent to subjects electronically or via postal service, and completed questionnaires may be returned to the site in the same manner. If subjects are unable to send completed questionnaires to the site, investigators should ask and record the subject's responses during the remote visit. • Patient Diary: Patient diaries may be sent to subjects electronically or via postal service. Completed diaries may be returned to the site in the same manner.	
Synopsis and Section 8.2.1	7. Subject is not of childbearing potential, i.e., a female who has not yet begun menstruating or who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason), hysterectomy or bilateral oophorectomy, combined oral contraceptives (estrogens and progesterone), or implanted or injectable hormonal contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline […]	7. Subject is not of childbearing potential, who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason), or has documented hysterectomy, **bilateral salpingectomy**, or bilateral oophorectomy. **For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.** OR Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees	Clarified definition of WOCBP. Clarified that a hormonal vaginal ring or an IUD inserted at least 30 days before Baseline is an acceptable form of contraception (i.e., IUD does not have to be hormonal). This change was requested from the RCH Human Research Ethics Committee (HREC) in Australia

	• Note: Subjects who are premenstrual at Screening but begin menses during the study should follow the pregnancy testing schedule for WOCBP and must abstain from sexual intercourse while in the study and for at least 1 month after the last study drug application.	to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception: • bilateral tubal ligation • combined oral contraceptives (estrogens and progesterone), **vaginal ring**, or implanted or injectable **hormonal** contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation • intrauterine device (IUD) inserted at least **30 days** before Baseline […]	
Synopsis and Section 8.2.2	4. Subjects with a known lipid disorder (hypertriglyceridemia >200 mg/dL, hypercholesterolemia >250 mg/dL. a. Subjects whose triglyceride and/or total cholesterol are within normal limits with stable dose of lipid-lowering agents for at least 6 months can be included.	4. Subject with **fasting triglycerides** >200 mg/dL **or >2.25 mmol/L and/or total cholesterol** >250 mg/dL **or >6.5 mmol/L**. Subjects whose triglycerides and/or total cholesterol are within normal limits with a stable dose of lipid-lowering agents for at least 6 months **may be** included.	To clarify laboratory parameters per laboratory units
	7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis).	7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis). **Subjects with hypothyroidism who are on a stable dose of thyroid hormone replacement therapy and whose TSH is normal may be included.**	To permit subjects with hypothyroidism on stable treatment with normal TSH to be enrolled.

	10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory b. Total bilirubin >1.1 mg/dL at screening, or, in case of Gilbert's syndrome total bilirubin >3 mg/dL	10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal **(ULN)** defined by the laboratory b. Total bilirubin **>1.25** × ULN at Screening. **Subjects with known** Gilbert's syndrome **may be included with total bilirubin >1.25 × ULN**	To clarify laboratory parameters for exclusion
	13. Subject has a history of long QT syndrome or has clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, or QTcF interval >450 ms, PR interval is not between 120 and 220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed	13. Subject has a history of long QT syndrome or has clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, or QTcF interval >450 ms	To clarify because there is a high number of left anterior hemiblocks without clinical significance among screened subjects. In these cases, the QRS Interval can be above normal
Synopsis	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Extension dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 200 µg/g applied topically twice weekly on up to 90% BSA	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: Up to 36 g per dose of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Extension dose, route, frequency: Up to 36 g per dose of 200 µg/g applied topically twice weekly on up to 90% BSA	Fixed dose is no longer applicable.
Synopsis and Section 10		Added: coagulation panel to all visits at which blood and urine are collected for laboratory tests	To correct an omission

Synopsis and Section 10.1.1	1. Screening: Up to 35 days (after signing informed consent, if necessary, washout may be up to 3 months, and subjects should return to the site after washout to complete the study eligibility requirements). 2. Double-blind study drug application: Twice weekly for up to 12 weeks. 3. Optional Open-label Extension: Twice weekly for up to 12 weeks. 4. Follow-up: 14 days after last study drug application. The maximum study duration for each subject is approximately 229 days (33 weeks). The maximum treatment duration for each subject is 24 weeks	1. Screening: Up to **97 days. Before asking a subject to enter washout, investigators should confirm the subject meets study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days**. **After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined** 2. Double-blind study drug application: Twice weekly for **90 days**. 3. Optional Open-label Extension: Twice weekly for **90 days**. 4. Follow-up: 14 days after last study drug application. The maximum treatment duration for each subject is approximately **90 days for subjects who choose not to continue into the OLE, and 180 days for those who choose to continue.** The maximum study duration for each subject is approximately **291 days**	To reflect the change from weeks to days, and to allow sufficient time for the washout period (up to 3 months) and adjust the study periods accordingly
Synopsis and Section 13.1.4.1	Secondary: The secondary endpoints are as follow: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Week 12: ▪ 5-point VIIS scale for scaling from Baseline through Week 12 ▪ Individual score for roughness (Scale: 0–4) overall • The difference in proportion of subjects with presence of fissures on palm/soles	Secondary: The secondary endpoints are as follow: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through **Day 90**: ▪ 5-point VIIS scale for scaling ▪ Individual score for roughness (Scale: 0–4) • The difference in proportion of subjects with presence of fissures on palm/soles (presence/absence, number of fissures, and pain	To reflect the change from weeks to days

	(presence/absence, number of fissures, and pain associated with fissures [on a 0-3 scale]) at Week 12 between the active trifarotene cream HE1 and vehicle groups	associated with fissures [on a 0-3 scale]) at **Day 90** between the active trifarotene cream HE1 and vehicle groups	
Synopsis and Section 13.1.4.1	Safety endpoints: – Local tolerability (Scale: 0-3 [none, mild, moderate, severe], determined by the investigator) for each body area (chest/abdomen, back, legs, arms, and face/neck).	Safety endpoints: – Local tolerability (**stinging/burning, pruritus, or erythema on 0-3 scales** [none, mild, moderate, severe]) for each body area (chest/abdomen, back, legs, arms, and face/neck).	
Table 2-1		Coagulation panel was added at Baseline, Day 30, and Day 90 Dispense study drug and diaries was added at Day 90 Added footnote: d Although it is preferable to conduct all necessary study assessments in person (on-site visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 and unscheduled visits may be conducted remotely. Screening and baseline visits must be performed onsite only, and must be postponed or scheduled for when onsite visits can be safely conducted.	To clarify when procedures are to be done To provide procedural accommodations due to COVID-19
Table 2-2		Vital signs (blood pressure and pulse) was added at Day 150 Ectropion score was added at Day 150 and removed at Day 134. Coagulation panel was added at Day 120 and Day 180 Added footnote: a. Although it is preferable to conduct all necessary study assessments in person	To clarify when procedures are to be done To provide procedural accommodations due to COVID 19

		(onsite visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 7-11 and unscheduled visits may be conducted remotely.	
Section 5.2	Throughout the 30 clinical studies that comprise the clinical development program for CD5789 topical products, 1976 subjects were exposed to CD5789	Throughout the **31 completed** clinical studies that comprise the clinical development program for CD5789 topical products, **4878** subjects were exposed to CD5789	Updated for latest data
Section 6.2	To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.	To assess safety for up to **180 days** of dosing **with trifarotene cream HE1 200 µg/g**.	Subjects will only receive open-label trifarotene cream HE1 200 µg/g for 90 days.
Section 10.2.4	Subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 12-weeks of double-blind treatment may choose to continue into an optional. During the OLE, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and Week 24 from all subjects who continue into the OLE (Table 2-2).	Subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 90 days of double-blind treatment may choose to continue into an optional 90 day OLE with trifarotene cream HE1 200 µg/g. During the OLE, subjects will return to the site at **Days 104**, **120, 150, 180, and 194**. Additional PK samples will be drawn at **Days 120** and **180** from all subjects who continue into the OLE.	To be more precise with timing
Section 7.2	To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of 15 subjects randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly.	To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of subjects randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly.	To allow flexibility in enrollment numbers.
Section 8.4	8.4 Discontinuation of Study Intervention Discontinuation from study treatment does not mean withdrawal from the study, and the remaining study procedures should be completed as indicated in the study protocol (see Section 10.2.4.5)	8.4. Subject Discontinuation of Study Intervention **and Stopping Rules** **Subjects who discontinue the study treatment will be asked to return to the site to undergo ET procedures (Section 10.2.4.6)**	To clarify and to link to correct section.

Section 9.1		Added: Sodium benzoate, butylhydroxytoluene, and propylene glycol are excipients known to have a recognized action or effect to be declared on the labeling, according to the CHMP Annex to the excipients in labeling and package leaflet of medicinal products for human use (EMA/CHMP/302620/2017). These 3 excipients are being used in the trifarotene formulation at standard concentrations and are all necessary to ensure adequate protection of the formulation along and the shelf life.	To fulfill request by French CA
Section 9.2	For the Double-blind Treatment Period, a fixed dose (determined at Visit 2) of trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject. Subjects will continue treatment for up to 12 weeks For the OLE, all subjects will receive trifarotene cream HE1 200 µg/g and apply it the same fixed dose same manner as in the Double-blind Period for an additional 12 weeks.	For the Double-blind Treatment Period, trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject. Subjects will apply treatment for 90 days. For the OLE, all subjects will receive **open-label** trifarotene cream HE1 200 µg/g and apply it in the same manner as in the Double-blind Period for an additional **90 days**.	To remove fixed dose and allow dosing to be based on BSA Clarification and precision of timing Clarification and precision of timing
Section 9.3	After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply approximately the same amount of IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week, at least 3 days apart, on which to apply their IP (e.g., Tuesday and Friday), and maintain that regimen throughout the study. Subjects should not apply the IP on visit days until after the visit, unless they participate in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the predose PK blood draw.	After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week, **3 to 4 days apart**, on which to apply their IP, and maintain that regimen **each week** throughout the study (Table 9-1). **Subjects whose treatment day falls on a scheduled study visit** day should not apply the IP until after the visit. **Subjects who** participate in the PK substudy **should have their Day 30 Visit scheduled on a treatment day,** in which case the IP will be applied in	To specify that treatment applications should be 3 to 4 days apart, and that PK substudy subjects must visit the clinic on Day 30.

		the clinic on Day 30 after the predose PK blood draw. Added: **If the Day 30 Visit cannot be scheduled on a treatment day, the investigators should contact the medical monitor.**	
	If a subject misses an IP application, they should apply the IP as soon as they remember and record the date/time in the subject diary.	Added: **The next application should be 3 to 4 days apart and subjects should continue according to their new regimen.**	To specify treatment day interval
	Subjects who continue into the Open-label Extension will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the Double-blind Period for an additional 12 weeks	Subjects who continue into the OLE will receive trifarotene cream HE1 200 µg/g and apply in the same manner as in the Double-blind Period for **90 days**	To remove fixed dose and allow dosing to be based on BSA
		Added: Table 9-1: Sample Twice-weekly Dosing Schedule	To provide a visual example of dosing schedule options
Section 9.4		Deleted Section 9.4.1 Stopping Rules	Section was redundant with Section 8.4
Section 9.5	Study personnel will assess treatment compliance with IP regimens by weighing IP tubes before dispensing and upon return and by questioning the subject, at every postrandomization visit. A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, supplemented by tube weight. A subject who is not compliant (used 80–120% of IP tubes) will be counseled at each visit on the importance of using the IP as instructed.	Study personnel will assess treatment compliance with IP regimens **by weighing kits (tubes and boxes, but not leaflets)** before dispensing and upon return and by questioning the subject at every post randomization visit. **At baseline, the kit should be weighed before choosing the first tube for application by the study staff.** A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, **supplemented by amount of cream used derived from weighing the IP kits**. A subject who is not compliant (for example, used <80 or >120% of IP tubes **[which is more than what can be dispensed per tube at each application]),** the subject will be counseled at each visit on the importance of using the IP as instructed.	
Section 10.2.2.7	Subjects will have up to 7 days to decide to enter the OLE; if the subject chooses to continue into OLE, the following	If the subject chooses to continue into OLE, the	Subjects must decide by Day 90 if they want to continue into the OLE.

	additional procedures will be done: ….Remind subjects that at least 24 hours must have elapsed since IP application before the PK draws at the Week 16 and Week 24 Visits, and not to apply IP on visit days until after the visits.	following additional procedures will be done Revised: Remind subjects that at least 24 hours must have elapsed since IP application before the PK draws at the **Day 120** and **Day 180** Visits, and not to apply IP on visit days until after the visits.	
Section 10.2.4.1	Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and to remind subjects not to apply IP on visit days until after the visit.	Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and to remind subjects not to apply IP on visit **Days 120 and 180** until after the visit.	Day 120 and Day 180 include PK draws, so IP should be applied after the visit is complete.
Section 10.2.4.2	12. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit at the Week 16 and Week 24 Visits, and not to apply IP on visit days until after the visit.	12. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit **(Day 120) and if the Day 120** visit **coincides with a treatment day, wait** until after the visit **is complete** to apply IP.	To specify timing of IP application
Section 10.2.4.5		Added: 13. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit (Day 180) and if the Day 180 visit coincides with a	To specify timing of IP application

		treatment day, wait until after the visit is complete to apply IP.	
Section 10.2.4.7	10.2.4.7 Follow-up Evaluation – Open-Label Extension Week 26/Visit 11)	10.2.4.7 Follow-up Evaluation – Open-Label Extension (**Day 194 or 14 days after End of Open label Treatment** /Visit 11)	To be more specific
Section 10.4 and Synopsis		New section: 10.4. Procedural Adjustments Due to COVID-19 The coronavirus (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted to control the spread of the disease. It is recommended that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19. Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 (Double-blind Period; Table 2-1), Visits 7-11 (OLE Period; Table 2-2) and unscheduled visits may be conducted remotely. Screening and baseline visits must be performed onsite only, and must be postponed or scheduled for when onsite visits can be safely conducted. Appendix B details the procedures when it is inadvisable or not possible to conduct an onsite study visit.	To provide procedures/schedule for COVID-19 issues.
Section 11.2.1		Added: The Tolerability Assessments Form at each visit collects a numeric severity score by body area for	To specify how tolerability assessments are collected.

		erythema, stinging/burning, and pruritus. In addition, if skin irritation is more than the expected erythema, stinging/burning, and pruritus with the application of this topical retinoid (i.e., clinically relevant), please enter the application site reactions in the Adverse Event description section. If a diagnosis is known, record the diagnosis. If a diagnosis is known and there are other signs/symptoms that are not generally part of the main diagnosis, record the diagnosis and each sign/symptom on a separate line. If a diagnosis is not known, record each sign/symptom on a separate line. Examples are allergic contact dermatitis, sunburn, skin erosion, and swelling.	
Section 11.2.2.3	Dose reduced An indication that a medication schedule was modified by subtraction, either by changing or reducing the frequency, strength, or amount.	Dose reduced An indication that a medication schedule was modified by **reducing the frequency of application**	Dose cannot be reduced by changing the strength or amount.
Section 11.3.2	These findings must be reported on the Exposure in Utero form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.	Deleted: The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an SAE and AE form (entering the event temporarily as nonserious on both forms) provided by the sponsor or its designee. These findings must be reported on the **Pregnancy Data Collection Form** and forwarded to **Premier Research PV**. The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly. **In such case an additional form (Serious Adverse Event Report Form) must be filled out by the Investigator and provided to Premier Research**	Repetitive; AE forms not collected by pharmacovigilance

		Pharmacovigilance within 24h of knowledge of the pregnancy's serious outcome.	
Section 12		Added names and qualifications of the DSMB The DSMB committee members are as follow: • Univ. Prof. Dr. med. Steffen Emmert, Director at Clinic and Polyclinic for Dermatology & Venereology • Jeffrey Louis Sugarman, M.D., Ph.D. • Moise L. Levy, MD, Pediatric Dermatologist • Gabriele Accetta, Ph.D. Biostatistician	In accordance with French Ethics Committee
Section 13.1.1		Added: Deviations related to COVID-19 will also be evaluated in determining Per-protocol Population eligibility.	To provide COVID-19 information
Section 13.1.4		Added: Efficacy endpoints will be based on investigator assessment.	To specify that investigator assessment is primary for efficacy
Section 13.1.4.5		Added: Thorough assessment on the extent of missing data and procedural adjustments due to COVID-19 as it pertains to the primary and secondary efficacy endpoints will be conducted ahead of database lock and additional sensitivity analyses may be performed. Full details will be documented in the SAP.	To provide contingency methods for COVID-19 issues
Section 14.3		Added: Subjects may only be rescreened once 30 days or more after the original Screening Visit.	Subjects should be rescreened if the reason for SF is reasonably believed to have been resolved.
Appendix B		Added new Appendix B with Procedural Adjustments for COVID-19.	To provide guidance for remote visits during COVID-19

AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ATC	anatomical therapeutic chemical
AUC	area-under-the-curve
BMI	body mass index
BSA	body surface area
CFR	code of federal regulations
CI	confidence interval
C_{max}	maximum concentration
COVID-19	Coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressure
DLQI	dermatology life quality index
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end-of-treatment
ESS	ectropion severity score
FDA	Food and Drug Administration
GCP	good clinical practice
GEE	generalized estimating equations
HR	heart rate
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IND	investigational new drug
IP	investigational product
IRB	institutional review board

ABBREVIATION	EXPLANATION
ITT	intent-to-treat
IUD	intrauterine device
IWRS	interactive web response system
LI	lamellar ichthyosis
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
MMRM	mixed model of repeated measures
NCA	noncompartmental analysis
OC	observed case
OLE	open-label extension
OTC	over-the-counter
PG	propylene glycol
PK	Pharmacokinetic(s)
PoC	proof-of-concept
PP	per-protocol
QTc	QT interval corrected for heart rate
RARγ	retinoid acid receptor γ
RBC	red blood count
RR	respiratory rate
RXR	retinoid X receptor
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
TEAE	treatment-emergent adverse event
T_{max}	time of C_{max}
TSH	thyroid-stimulating hormone
UAE	unexpected adverse event
UADR	unexpected adverse drug reaction
ULN	upper limit of normal
US	United States
UV	ultraviolet
VIIS	Visual Index for Ichthyosis Severity
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

5. INTRODUCTION

5.1. Background and Rationale

The ichthyoses comprise a large group of skin scaling disorders with diverse etiology. The stereotypic pathophysiology is epidermal hyperplasia and the formation of excess stratum corneum accompanied by abnormal (delayed and/or disordered) desquamation, with visible accumulation of squames (scales) on the skin's surface – the clinical hallmark of all the ichthyoses.

Lamellar ichthyosis (LI) is recognized as a severe form of ichthyosis that persists throughout life. During the first postnatal weeks, the hyperkeratotic membrane patients are typically born with is gradually shed, and is replaced by scaling and lichenification that involves the entire body including the intertriginous areas, palms, soles, and scalp. While usually not life threatening, LI can result in disability, partial deafness, poor adaptation to environmental conditions (due to hypohydrosis), severe discomfort (pruritus, fissuring of the skin) and significant psychosocial impact.

Lamellar ichthyosis, a member of the nonsyndromic autosomal recessive congenital ichthyosis group of ichthyoses, has an incidence of 1 per 100,000-300,000 live births.[1] Lamellar ichthyosis is undoubtedly a rare disease.

Therapeutic approaches for LI are mainly based on the use of topical emollients, keratolytic agents (urea, lactic acid, salicylic acid), topical retinoids and, in severe cases, oral retinoids.[2,3]

Oral retinoid usage in LI is mainly based on case reports and case series.[4,5,6,7,8] The mechanism of retinoid action involves modulation of keratinocyte differentiation, keratinocyte hyperproliferation and tissue infiltration by inflammatory cells. Systemic retinoids (such as acitretin, etretinate, or isotretinoin) have been found to be efficacious in the treatment of severe ichthyoses, especially in LI.[6]

Vahlquist, et al (2008)[3] report that by combining 2 or more keratolytic agents and moisturizers in the same lipophilic cream base, it is often possible to achieve additive or even synergistic effects in LI without the need to use irritating concentrations of either agent alone. In a double-blind trial of 4 different cream mixtures in 20 patients with LI, a mixture of 5% lactic acid and 20% propylene glycol (PG) in a semi-occlusive cream for 4 weeks twice daily was significantly more effective than 20% PG or 5% urea alone in the same vehicle.[9] Although the treatments were well tolerated, an efficient removal of hyperkeratosis without correcting the underlying biochemical defect in LI is likely to deteriorate the patient's intrinsic barrier problem, because an excessive production of corneocytes probably represents a homeostatic response to an ineffective barrier. Indeed, transepidermal water loss increased after successful treatment of LI with either topical keratolytics[9] or oral retinoid.[10] Although this may not be noticeable by the patient, even minor deteriorations in the barrier function can enhance transcutaneous penetration of active cream ingredients or other topically applied chemicals, which is a matter of special concern in children. Accordingly, α-hydroxy acids and salicylic acid should not be used at all in babies and only with great caution when treating large, eroded skin areas in adult patients.[11,12]

Many patients with LI use pumice, foot files, or gentle rubbing of the skin after a hot bath or a shower to remove scales and hyperkeratosis. Overnight occlusion of problematic skin areas with plastic sheets after applying a thick layer of emollient or keratolytic agents is another way of potentiating therapy, especially on the scalp, which is notoriously difficult to treat. Although

usually effective, all these remedies may further damage the skin barrier and lead to exaggerated epidermal proliferation, erythema, painful erosions and increased transcutaneous penetration.[3]

Based on this information, LI has significant unmet medical need for safer and more effective therapies.

5.1.1 CD5789 (Trifarotene)

CD5789 is a new chemical entity discovered by Galderma R&D SNC and formulated for topical application. It is a novel retinoid acid receptor γ (RARγ) agonist, characterized by its high specificity to this receptor. CD5789 is selective for RARγ over RARα and RARβ (approximately 50- and 8-fold, respectively), with no retinoid X receptor (RXR) activity. CD5789 is currently under clinical development for the topical treatment of various dermatoses, including acne vulgaris and LI.

The pharmacological retinoid-like properties of CD5789 were confirmed in in vitro and in vivo models, showing its interest for its development in the treatment of LI. Therefore, it may have an effect on the differentiation and hyperproliferation of keratinocytes, and consequently improve hyperkeratotic skin of patients with lamellar ichthyosis.

Within the overall acne development program at Galderma, CD5789 has been tested in different pharmaceutical forms for topical administration. As of 15-Jan-2018, 6 different formulations have been evaluated: a solution, a gel and 4 creams (CD5789 cream A, CD5789 cream B, CD5789 cream HE1 concept and its optimized version, cream HE1), with different concentrations (up to 400 µg/g). Therefore, several formulations at different CD5789 concentrations have been tested in nonclinical and clinical development programs.

Galderma decided to develop a new cream formulation that might better address the issue of skin dryness in patients with LI. This formulation was named “Cream HE1 concept.” It has been preliminarily investigated in an exploratory trial in psoriasis at concentrations up to 400 µg/g (RD.03.SRE.40204E). In a proof-of-concept study (RD.03.SRE.40181E), positive results were also obtained in patients with LI with CD5789 cream (up to 100 µg/g) that was effective in decreasing scaling and roughness. Based on these results, a new CD5789 formulation (cream HE1) was developed for further clinical investigations in LI. The formulation cream HE1 was developed with the objective to obtain a formulation with appropriate stability of the active ingredient and in which CD5789 would be homogeneously dissolved in the oily phase at a higher concentration compared to the cream formulation used in the acne program. Cream HE1 contains 100, 200, or 400 µg/g (0.01% [w/w], 0.02% [w/w], 0.04% [w/w], respectively) of CD5789.

Galderma has granted Mayne Pharma LLC an exclusive license to develop and commercialize CD5789 (trifarotene) for LI and other orphan diseases; therefore, the LI indication is no longer pursued by Galderma.

5.2. Clinical Experience

The cream HE1 differs from the CD5789 cream used to treat acne vulgaris in that it contains fewer excipients with drying effects and therefore may be better suited for patients with LI.

Throughout the 31 completed clinical studies that comprise the clinical development program for CD5789 topical products, 4878 subjects were exposed to CD5789. No systemic safety concerns related to CD5789 gel or creams, or cream HE1 at doses up to 400 µg/g were reported. The subjects

were exposed to a maximal total CD5789 dose of 36 g/day (Investigator's Brochure for CD5789 Cutaneous Formulation).

One study was conducted with CD5789 50 μg/g, 100 μg/g, and placebo in subjects with ichthyosis (Study RD.03.SRE.40181E). Among 31 subjects treated in this study, 17 were treated with CD5789 100 μg/g, and 14 were treated with 50 μg/g (all subjects received placebo [vehicle] on the contralateral zone). Mean (SD) baseline IGA score was 5.7 ± 1.6 among the 31 subjects. Improvement in the investigator's global assessment (IGA) of scaling and roughness was observed by Day 8 with both doses. The primary efficacy criterion was the change in IGA from the Baseline Visit (Day 1) to the Final Visit (Day 43). At Endpoint (intent-to-treat population, last observation carried forward [LOCF]), the CD5789 100 μg/g group had a statistically significant decrease from Baseline in IGA compared with Vehicle (-1.4±2.2; p=0.018) (Investigator's Brochure for CD5789 Cutaneous Formulation).

The CD5789 PK profile was also investigated using cream HE1 (Study GD.03.SRE.103813) in 36 healthy volunteers of Japanese and non-Japanese origin. Subjects were treated daily on up to 90% of body surface area (BSA) for 29 days with up to 36 g of cream formulation. Both CD5789 100 μg/g and 200 μg/g cream HE1 were investigated. Plasma PK assessment demonstrated that repeated topical applications of CD5789 cream HE1 resulted in low and similar CD5789 systemic levels in all treatment groups. In addition, no systemic safety concerns were raised from this healthy volunteer study in which cream HE1 200 μg/g was applied daily under maximal-use conditions on almost the full body. In this study, however, the level of irritation resulted in the need to decrease the frequency of application to twice weekly (Investigator's Brochure for CD5789 Cutaneous Formulation). However, it is possible that absorption in subjects with LI may be greater than in healthy volunteers, due to the skin being compromised.

Based on these data, both the 100 μg/g and 200 μg/g doses showed an acceptable safety profile and will be used in this phase 2 LI study, to determine which of the 2 doses is most effective. The open-label extension (OLE) will evaluate the long-term safety of the higher dose in this patient population.

5.3. Summary of Potential Risks and Benefits

Although the primary objective of this study is safety in the patient population with LI, the potential benefits of study participation are that subjects with LI may experience a reduction in their LI symptoms as a result of treatment with trifarotene (CD5789) cream HE1. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to trifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture.

Animal studies with CD5789 have shown reproductive toxicity in the embryo-fetal studies. Despite low systemic levels with the CD5789 concentration of 50 μg/g used in patients with acne, CD5789 must not be administered during pregnancy.

When CD5789 is used in the other formulations and/or for other indications and/or with higher concentrations or higher application surface areas, the potential risk of teratogenicity needs to be considered as the safety margin may be lower. Depending on the study population and conditions mentioned above, or other specific requirements, the appropriate contraception method is described in this protocol.

It is unknown whether CD5789 or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Lactating women are not eligible for the clinical study.

Certain cutaneous signs and symptoms of irritation and localized reactions at the application site such as erythema, scaling, dryness, stinging/burning, and pruritus may be experienced with use of CD5789. Depending upon the severity of these side effects, subjects may be instructed to reduce the frequency of application or to discontinue use.

Trifarotene cream contains propylene glycol that is mildly irritant to the skin, eyes, and mucous membranes. Trifarotene (CD5789) cream HE1 also contains butylated hydroxytoluene that may cause local skin reactions (e.g., contact dermatitis), or irritation to the eyes and mucous membranes and sodium benzoate that is mildly irritant to the skin, eyes, and mucous membranes.

CD 5789 is mildly irritant to the skin, eyes, and mucous membranes. Therefore, it should not come into contact with the eyes, mouth, or mucous membranes.

There is a potential risk of skin sensitization. If a reaction suggesting sensitivity to trifarotene (CD5789) cream HE1 occurs, the use of the trifarotene cream HE1 must be discontinued.

There is a potential risk of photosensitivity disorder (sunburn). Excessive exposure to sunlight or ultraviolet (UV) radiation (i.e., occupational exposure to the sun, planned holidays in the sun during the study, phototherapy, tanning salon) must be avoided during the studies. In addition, subjects should take protective measures such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet) and/or seeking shade or shelter from the sun.

As reported with other topical retinoids, there is a potential risk of pigmentation disorders.

No clinically significant systemic risks associated with CD5789 have been identified. Given the mechanism of action for CD5789 Cream HE1, it is assumed that efficacy will increase as the dose is increased. As such, the 200 µg/g dose was selected for the OLE based on its previously established safety profile, expected superiority to placebo and 100 µg/g. However the Data Safety Monitoring Board (DSMB), who will routinely review aggregate safety and tolerability data, as well as any safety concerns brought to the their attention by the study investigators or medical monitor, may determine that the study should be modified, placed on hold, or stopped if serious safety issues are discovered. This is applicable for both the double-blind portion and OLE. If the 200 µg/g dose in raises any safety concerns, the protocol will be amended and the dose will be reduced.

A summary of the pharmaceutical properties and known potential risks of trifarotene (CD5789) cream HE1 is provided in the current version of the investigator's brochure (IB). The investigator must become familiar with all sections of the trifarotene (CD5789) cream IB before the start of the study.

6. OBJECTIVES

6.1. Primary Objective

The primary objective is to compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in subjects with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 90 days of treatment.

6.2. Secondary Objectives

The secondary objectives are as follows:

- To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% BSA twice weekly.
- To assess safety for up to 180 days of dosing with trifarotene cream HE1 200 µg/g.

7. STUDY DESIGN

7.1. Overall Study Design and Plan

The first part of this study is a phase 2, randomized, 2-cohort, double-blind, vehicle-controlled, multicenter study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in subjects with LI for 90 days. Subjects who complete the randomized, double-blind, vehicle-controlled period of the study will be eligible to continue into an open-label extension (OLE) and be treated with trifarotene cream HE1 200 µg/g for an additional 90 days.

The randomized, double-blind, vehicle-controlled period of the study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Investigator Global Assessment [IGA] scale where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe), is designed to compare the safety of 2 doses of trifarotene cream HE1 with that of vehicle in the treatment of LI.

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods (Table 9-2), as applicable. Washout may be up to 90 days, as necessary.

During washout, subjects may continue taking their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard-of-care treatments in the electronic case report form (eCRF). If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower, but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline. After completing any necessary washout of prohibited medications, subjects will return to the site to have their LI assessed and to complete the study eligibility requirements.

Study drug will be packaged in 50-g tubes from which up to 36 g of IP may be dispensed per application, i.e., the maximum dose per application.

Study staff will choose 1 tube from the kit dispensed to the subject at that visit, and apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements; they will

weigh the study tube before and after application to determine the amount used. If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.

The kit dispensed at baseline must be weighed before the first tube is chosen for application by the study staff. Weight of the kits dispensed and returned by the subject during the study includes both tubes and cartons, but not leaflets, which need to be removed before weighing. The subject must be reminded to return the kits with tubes and cartons, whether used or not, when returning to the next visit.

Thereafter, subjects will apply up to 36 g of study drug on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of IP in a tube.

The study protocol limits application of IP to 36 g maximum; no additional tubes can be given, whether during the randomization period or the OLE period. If the study staff and subject note that there is insufficient volume for full body application, the subject should apply trifarotene cream sparingly twice weekly to the most affected areas, and always to the same skin areas. Study cream should be very sparingly applied. Trifarotene cream 100 or 200 µg/g, is a highly potent topical retinoid and it is not necessary to apply much for efficacy; application of more will increase the risk of irritation and systemic penetration.

Enrolled subjects will receive treatment for 90 days.

The first cohort of subjects (Cohort A) will randomize adults (≥18 years old) in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle.

After the initial 15 subjects complete at least 28 days of treatment, an independent DSMB will review aggregate safety and tolerability data (including PK and electrocardiogram [ECG] data). If no safety issues are identified, additional subjects will be allowed to enroll in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and similarly treated twice weekly for up to 90 days in the same manner as subjects in Cohort A.

Cohort A will continue enrolling subjects until the DSMB considers it safe to open recruitment in Cohort B.

All subjects will be given diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]), any application site reactions, adverse events (AEs), and concomitant medications used. Subjects will also be advised on permitted emollient(s) and/or sunscreen(s) use on nontreatment days during the study; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited.

At all sites with photographic capability, photographs will be taken as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional, photographic informed consent form (ICF).

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit, as indicated in the Schedule of Events (Table 2-1). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application. Subjects should not apply IP on visit days until after the visit.

In addition, a PK substudy will be conducted on Days 1 and 30 at sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 30 subjects. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for all subjects at specified time points. For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30.

Efficacy will be assessed by the number of subjects in each treatment group who achieve "success" defined as clear/almost clear overall and at least a 50% reduction from Baseline at Day 90/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA scale (i.e., 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe). In addition, efficacy criteria include assessment scales for palm/sole, scaling, roughness, fissuring, and the Dermatology Life Quality Index (DLQI), and the EQ-5D Quality of Life (QoL) Questionnaire. Ectropion Severity Scores (ESS) between the active trifarotene cream HE1 and vehicle groups will be an exploratory endpoint.

Plasma concentrations of CD5789 and its major metabolites will be measured.

Safety will be assessed by evaluating reported adverse events (AEs), changes in clinical laboratory test results, vital sign measurements, physical examinations, 12-lead ECGs, and local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]).

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent through the post-treatment visit) will be documented.

Topical trifarotene cream HE1 was generally well tolerated in recently completed phase 3 pivotal and long-term safety studies in subjects aged 9 years and older with acne vulgaris. The local tolerability of the trifarotene cream HE1 formulation in subjects with LI is unknown and will be monitored during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. At each clinic visit, the investigator will assess local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]) on each treated body area (chest/abdomen, back, legs, arms, and face/neck).

All subjects (Cohort A and Cohort B) who complete the 90-day Double-blind Treatment Period will be eligible to enroll in the 90-day OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly. During the OLE, subjects will return to the site at Days 104, 120, 150, 180, and 194. Additional PK samples will be drawn at Days 120 and 180 from all subjects who continue into the OLE (Table 2-2).

Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and AEs; see Section 9.4.

Figure 7-1: Double-blind Study Design

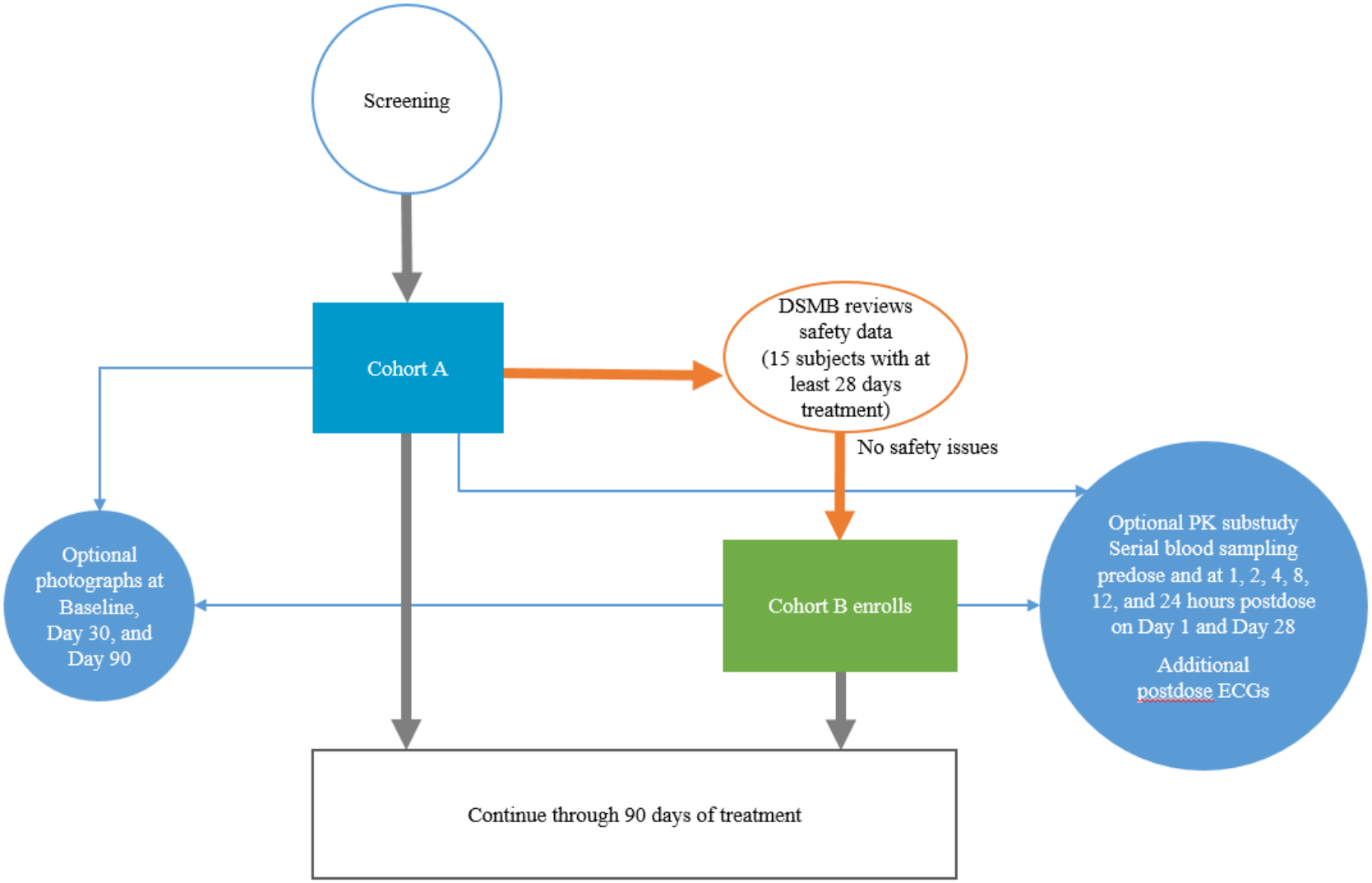
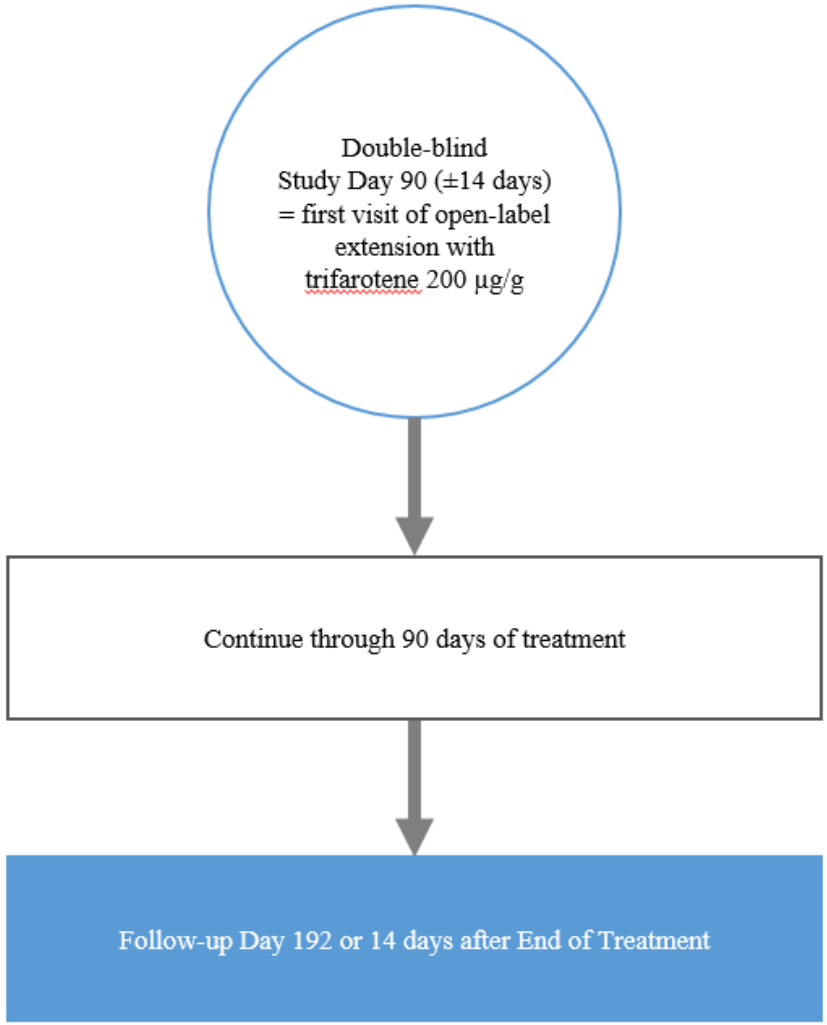


Figure 7-2: Open-label Study Design



7.2. Rationale and Discussion of Study Design

The first part of this study is a randomized, double-blind, placebo-controlled study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in subjects with LI.

In a previous proof-of-concept study (RD.03.SRE.40181E), subjects with LI applied trifarotene 50 and 100 µg/g cream to limited areas and results demonstrated a decrease in scaling with good safety and tolerance. In a phase 1 study in healthy Japanese and non-Japanese subjects (RD.03.SPR.103813), repeated topical applications of trifarotene (CD5789 cream HE1) 100 µg/g and 200 µg/g resulted in low and similar CD5789 systemic levels in all the cohorts. These studies are fully described in the current IB.

To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of subjects randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly. An independent DSMB will review aggregate safety and tolerability data from the initial 15 subjects' first 28 days of treatment. If no safety issues are identified, additional subjects will be allowed to enroll in Cohort B and randomized to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly in the same manner as subjects in Cohort A. All subjects in the randomized, double-blind portion of the study will be treated for up to 12 weeks and data on safety, tolerability, PK, and efficacy collected.

Subjects who successfully complete the initial 90 days of double-blind treatment will have the option to enter an OLE with trifarotene cream HE1 200 ug/g twice weekly for up to 90 days.

The OLE will collect additional safety, tolerability, PK, and efficacy data. As designed, this study will provide important information on safety, tolerability, and PK with dosing of subjects with LI for up to 180 days.

The protocol includes appropriate monitoring for safety and tolerability. If subjects develop significant local application site reactions or tolerability issues, the protocol includes language for reducing the frequency of application or halting study drug application until the symptoms abate.

7.3. Selection of Doses in the Study

Based on the results from Study RD.03.SRE.40181E and Study SRE.103813, the doses of 100 µg/g and 200 µg/g were selected for further investigation in subjects with moderate to severe LI to determine which of the 2 doses is most effective. The proof-of-concept (PoC) study demonstrated efficacious treatment with 100 µg/g in adults. The PK and tolerability study showed that, when the frequency of application was reduced from daily to twice weekly, the 200 µg/g cream HE1 had good local tolerability.

Therefore, the current study will use these doses compared with vehicle, applied twice weekly on up to approximately 90% BSA in subjects with LI. The OLE will evaluate the long-term safety of the higher dose in this patient population.

7.4. Study Sites

The study will take place at approximately 40 sites in North America, Europe, Israel, and Australia.

7.5. Point of Contact

A point of contact will be identified to provide information to subjects about where to obtain information on the study, the rights of subjects, and whom to contact in case of a study-related injury. This information will be provided in the subject information and informed consent form (ICF).

7.6. End of Study Definition

A clinical trial is considered completed when the last participant's last study visit has occurred.

8. SUBJECT POPULATION

8.1. Selection of Study Population and Diagnosis

Diagnosis of LI for the purposes of this study will be a clinical diagnosis. Although some younger subjects may have had genetic testing, older subjects may not.

While LI is a rare disease and subject enrollment may be challenging, due to possible bias introduced by including household members in the same study, it is recommended that only 1 household member be included in the study to maintain the blind and ensure all assessments are independent.

8.2. Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. Subject is ≥18 years old.
2. Subject has known diagnosis of LI.
3. Subject has moderate to severe (IGA 3–4) LI on the IGA of LI severity.
4. Subject has signed an ICF at Screening before any investigational procedures.
5. Subject who is participating in optional photography has signed a photography ICF.
6. Subject who is participating in the optional PK substudy has signed a PK ICF.
7. Subject is not of childbearing potential, i.e., a female who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason), or has documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   OR

   Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception:

   - bilateral tubal ligation

- combined oral contraceptives (estrogens and progesterone), vaginal ring, or implanted or injectable hormonal contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation
- intrauterine device (IUD) inserted at least 1 month before Baseline

OR

Agrees to abstain from heterosexual intercourse during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

AND

Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application.

8. Women of childbearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine).
9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent.
10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

8.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization, including syndromic ichthyoses.
2. Subject has current moderate or severe stinging/burning at Screening.
3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments.
4. Subject with fasting triglycerides >200 mg/dL or >2.25 mmol/L and/or total cholesterol >250 mg/dL or >6.5 mmol/L. Subjects whose triglycerides and/or total cholesterol are within normal limits with a stable dose of lipid-lowering agents for at least 6 months may be included.
5. Subject was previously treated with trifarotene/CD5789 in an acne or ichthyosis study.
6. Subject has any other significant concomitant disease, or poorly controlled medical condition other than LI that in the investigator's opinion may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis). Subjects with hypothyroidism who are on a stable dose of thyroid hormone replacement therapy and whose thyroid-stimulating hormone (TSH) is normal may be included.

8. Subject is being treated for major depression disorder and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts.
9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening.
10. Subject with any of the following laboratory values at Screening:
    a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal (ULN) defined by the laboratory
    b. Total bilirubin >1.25 × ULN at Screening. Subjects with known 1 mg/dL or, in case of Gilbert's syndrome may be included with total bilirubin >1.25 × ULN
    c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women
    d. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L.
11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
12. Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment.
13. Subject has a history of long QT syndrome or has clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, or QTcF interval >450 ms.
14. Subject has a known allergy or sensitivity to any of the components of the investigational products.
15. Subject has been exposed to excessive UV radiations on the treated zones within 1 month before Baseline visit or is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.).
16. Subject is inherently sensitive to sunlight.
17. Subject is unable or unwilling to stop use of topical or systemic retinoids.
18. Subject is presumed to be abusing drug or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms.
19. Subject is participating in another interventional clinical trial.
20. Subject is institutionalized.
21. Subject is in any way related to the sponsor, investigator, or site personnel.

8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

8.4. Subject Discontinuation of Study Intervention and Stopping Rules

Subjects who discontinue the study treatment will be asked to return to the study site to undergo ET procedures (see Section 10.2.4.6). If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

An investigator must discontinue a participant's study treatment for any of the following reasons:

- Pregnancy
- Significant study intervention noncompliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would result in a significant burden to the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for discontinuation of study treatment will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized, and receive the study intervention, and subsequently discontinue study treatment, or are withdrawn from the study will not be replaced.

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.5. Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Randomized subjects withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

9.1. Identification of Investigational Product(s)

Trifarotene cream HE1 is a cream containing 100 or 200 µg/g (0.01% [w/w] or 0.02% [w/w], respectively) of CD5789 and the following excipients: purified water, propylene glycol, allantoin, glycerin, medium-chain triglycerides, polypropylene glycol 15 stearyl ether, cyclomethicone, phenoxyethanol, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane (simulgel 600 PHA), sodium benzoate, butylated hydroxytoluene, and gluconolactone. It is an RARγ agonist characterized by its high specificity to this receptor.

Sodium benzoate, butylhydroxytoluene, and propylene glycol are excipients known to have a recognized action or effect to be declared on the labeling, according to the Committee for Medicinal Products for Human Use Annex to the excipients in labeling and package leaflet of medicinal products for human use (EMA/CHMP/302620/2017). These 3 excipients are being used in the trifarotene formulation at standard concentrations and are all necessary to ensure adequate protection of the formulation along and the shelf life.

Vehicle contains the same ingredients, without the CD5789.

Trifarotene cream HE1 and vehicle will be provided in cream form for topical application and will be supplied in 50-g tubes from which a maximum of 36 g of IP may be extracted.

Trifarotene cream HE1 and vehicle will be supplied by G. Production, Inc. (Galderma) in Baie-D'Urfé, QC, Canada.

9.2. Treatments Administered

For the Double-blind Treatment Period, trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject. The IP should be applied thinly and gently rubbed in.

Study staff will apply the first administration of IP in the clinic on Day 1 after Baseline measurements, and the amount of IP used will be measured (i.e., 50-g tube will be measured before and after application to determine amount used). If the product will be applied at home by someone other than the study subject, it is recommended that this person assist with application at the first visit to learn how the IP is applied.

The maximum dose per application is 36 g (i.e., 1 tube). Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than full amount of product in a tube. Subjects will apply treatment for 90 days.

After the Day 1 visit, subjects will apply up to 36 g of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Persons other than the study subject applying the study drug must wash their hands after application or use disposable vinyl gloves. In addition, a long-handled applicator will be provided for application on the back. The applicator must be washed with warm water and soap after every application.

Trifarotene cream should not come into contact with the eyes, mouth, angles of the nose, or mucous membranes. For the ectropion treatment, Q-tips are recommended for precise application on eyelids, without contact to the eye or conjunctiva. If the IP gets into the eye, it must be flushed

immediately with warm water. In case of eye irritation, the subject must be seen by an ophthalmologist.

For the OLE, all subjects will receive open-label trifarotene cream HE1 200 µg/g and apply it in the same manner as in the Double-blind Period for an additional 90 days.

Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application. Subjects should not apply IP on visit days until after the visit, unless they are participating in the PK substudy, in which case the IP will be applied in the clinic on Day 1 and Day 30 after the blood draw. Among subjects participating in the PK substudy, ensure the PK line is inserted before study drug application to prevent contamination with the IP and to protect the skin around the needle insertion point from study drug application.

9.3. Selection of Timing of Dose for Each Subject

Subjects will be randomized in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week 3 to 4 days apart on which to apply their IP, and maintain that regimen each week throughout the study (Table 9-1). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained on the skin after the last application. Subjects whose treatment day falls on a scheduled study visit day should not apply the IP until after the visit. Subjects who participate in the PK substudy should have their Day 30 Visit scheduled on a treatment day, in which case the IP will be applied in the clinic on Day 30 after the predose PK blood draw. If the Day 30 Visit cannot be scheduled on a treatment day, the investigator should contact the medical monitor.

All subjects will be provided with diaries in which to record study drug application (days/times) and any areas of skin not treated (e.g., due to local reactions).

If a subject misses an IP application, they should apply the IP as soon as they remember and record the date/time in the subject diary. The next application should be 3 to 4 days apart, and subjects should continue according to their new regimen.

Subjects should not shower, bathe, or swim for at least 4 hours after IP application. No occlusive dressings should be used on areas to which IP is applied.

Subjects who continue into the OLE will receive trifarotene cream HE1 200 µg/g and apply it in the same manner as in the Double-blind Period for an additional 90 days.

Table 9-1: Sample Twice-weekly Dosing Schedule

	Week 1							Subsequent Weeks						
	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Option 1	X			X				X			X			
Option 2		X			X				X			X		
Option 3			X			X				X			X	
Option 4				X			X				X			X
Option 5	X				X			X				X		
Option 6		X				X			X				X	
Option 7			X				X			X				X

9.4. Dose Adjustment Criteria

Local tolerance will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]) for each treated body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed:

- If a score of 2 (moderate) is recorded for any of the local tolerability assessment scales (stinging/burning, pruritus, or erythema) on any treated area (e.g., the face), the study drug will be applied on this area only once weekly, until the score returns to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas.
- If a score of 3 (severe) is recorded for any of the local tolerability assessment scales (stinging/burning, pruritus, or erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas.

Any changes in dosing must be documented in the subject diary and the eCRF.

9.5. Treatment Compliance

Subjects will be asked to record their twice-weekly applications of IP in the diary during both the Double-blind Period and the OLE. Deviations from the planned doses (missed dose or timing) will be recorded on the subject's eCRF. Study personnel will review diaries at each visit and diaries will be collected as source documents. Information from subject diaries will be transcribed on the appropriate eCRF pages for documentation of subject compliance with the IP.

Study personnel will assess treatment compliance with IP regimens by weighing kits (tubes and boxes, but not leaflets) before dispensing and upon return and by questioning the subject, at every postrandomization visit. At Baseline, the kit should be weighed before choosing the first tube for application by the study staff. A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, supplemented by amount of cream used derived from weighing the IP kits. A subject who is not compliant (for example, used 80-120% of IP tubes [which is more than what can be dispensed per tube at each application]) will be counseled at each visit on the importance of using the IP as instructed.

Subjects who taper to once-weekly application or who take a "drug holiday" for tolerability will not be reported as having deviated from the protocol (see Section 9.4 for dose adjustment and stopping rules); any changes in dosing must be documented in the subject diary and the eCRF.

9.6. Method of Assigning Subjects to Treatment Groups

In the double-blind, parallel-group, randomized period of the study, subjects who meet study entry criteria will be randomly assigned in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. Study center will not be a blocking factor in the randomization schedule.

Premier Research will prepare the randomization schedule before the start of the study. No one involved in the study performance will have access to the randomization schedule before the official unblinding of treatment assignments. No subject will be randomized into this study more than once.

In the OLE, all subjects will receive trifarotene cream HE1 200 µg/g.

9.7. Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the Double-blind Period of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician and programmer from Premier Research who will have access to the randomization code. The statistician will have access to unblinded data if there is an unblinded DSMB review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

The investigator may discuss with the medical monitor in advance of unblinding a subject, if possible, if it is not deemed an emergency. However, the investigator has the ultimate decision for unblinding a subject for medical treatment and no procedures will prevent or delay necessary unblinding in an emergency for the subject's safety. For emergency unblinding, study personnel will use the IWRS code. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

The primary analysis period is the first 90 days of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after database lock has been achieved. A second analysis will take place for endpoints assessed from Day 90 through the OLE.

9.8. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

Upon signing informed consent and entering the Screening Period, subjects may begin a Washout Period of up to 90 days. Participants will stop using physical and medical treatments for LI,

including balneotherapy, as well as the following prohibited medications, as applicable (Table 9-2).

Table 9-2: Washout Periods for Prohibited Medications[a]

Medication	Washout Period
Topical Treatments	
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	2 weeks
Systemic treatments	
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones unless the dose is stable and TSH is normal, cytotoxics, bisphosphonates, selective estrogen receptor modulators (SERM), teriparatide, calcitonins, tetracyclines, quinolones, thiazides, long-term salicylates, heparin, theophylline, barbiturates, colchicines. Vitamin D analogs taken at stable dose for at least 1 month are allowed)	8 weeks
QT-prolonging drugs	5 half lives
CYP Enzyme inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (including, but not limited to the following: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives
Monoclonal antibodies	5 half lives

a Note: This list applies to both prescription and over-the-counter (OTC) medications

During washout, subjects may continue their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard-of-care treatments in the eCRF. If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower, but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.

After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.

9.8.1 Permitted Therapies

Subjects will be advised on permitted emollient(s) for use as often as needed on nontreatment days during the study; on treatment days, the use of emollient(s) is permitted except within 4 hours before or after study drug application. Similarly, protective sunscreen should be applied as often as needed, except within 4 hours before or after study drug application. Subjects may use their standard of care treatment on their faces and/or palms/soles after the Day 30 assessment if they

experience a worsening of IGA in those areas. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. These standard of care treatments should be approved by the investigator and documented in the eCRF.

Subjects who enter the OLE must stop standard of care treatment. If they experience a worsening of IGA they may use standard of care treatment on their faces and/or palms/soles after the Day 120 Visit if the standard of care does not contain prohibited medications. If those standard of care treatments include prohibited medications, the subject should be discontinued from the study.

Other concomitant medications are allowed (e.g., analgesics, antihistamines), but should be limited to those medications considered necessary. All concomitant medications, both prescribed and over-the-counter, should be recorded in the eCRF.

9.8.2 Prohibited Therapies

The medications listed in Table 9-2 are prohibited during the study. Balneotherapy is also prohibited during the Screening Period and during the study.

Subjects may not use concomitant keratolytics such as urea, salicylic acid, alpha, or beta hydroxyacids. Subjects may not use topical or systemic retinoids. Subjects may not take more than 3500 IU/day Vitamin A (e.g., as in a multivitamin). Use of benzoyl peroxide is permitted on nontreatment days for subjects with concomitant acne only); it must not be applied on treatment days due to risk of inactivation of trifarotene by benzoyl peroxide.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continued treatment in the study, at the investigator's discretion with consultation with Mayne Pharma LLC and the medical monitor. For enrolled subjects who require prescription of a systemic azole, the principal investigator should discuss with the medical monitor whether the subject may continue in the study.

9.8.3 Restrictions

Subjects should not shower, bathe, or swim for at least 4 hours after study drug application. No occlusive dressings should be applied to areas where study drug was applied.

Subjects should only use investigator-approved emollients and should not use them on treatment days within at least 4 hours before and after study drug application.

In addition, subjects should take protective measures to avoid exposure of treated areas to sunlight, such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet), and/or seeking shade or shelter from the sun.

9.9. Treatment after End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.10. Dispensing and Storage

The test product supplied by Mayne Pharma LLC is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Premier Research. Until the IP is dispensed to the subjects, it must be stored at 20–25°C (68–77°F), with excursions permitted to 15–30°C (59–86°F); do not freeze and with the tube kept tightly closed in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

9.11. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of subjects (subject number) who received the IP. The investigator will not supply the IP to any person except those named as subinvestigators on the Form Food and Drug Administration (FDA) 1572, designated study personnel, and subjects in this study. The investigator will not dispense the IP from any study sites other than those listed on the Form FDA 1572. Investigational product(s) may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Each subject will be given enough tubes of study drug to apply up to 1 tube-full (approximately 36 g of clinical trial material) per treatment day until the next study visit. Tubes will be packed 2 to a carton, and each subject will receive enough cartons to have the maximum number of tubes needed until the next study visit. The number of study drug tubes the subject needs to provide enough IP until the next visit is shown in Table 9-3.

Table 9-3: Amount of Study Drug Needed Per Visit

Treatment Period	Number of Cartons	Number of Tubes
Double-blind Treatment Period		
Baseline	3	6
Day 14	4	8
Day 30	6	12
Day 60	6	12
OLE		
Day 90	3	6
Day 104	4	8
Day 120	6	12
Day 150	6	12

Each carton will be weighed before dispensing (tubes and boxes, but not leaflets) and subjects are to bring all cartons and tubes back at each study visit, whereupon study staff will weigh them again to estimate study drug use and compliance.

Upon completion of the study, the IP (partly used, unused, and empty tubes) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.12. Labeling and Packaging

Labeling and packaging of IP will be performed by Catalent Pharma Solutions.

Tubes will be packaged in cartons comprising 2 tubes each. Tubes will be labeled with inner and outer booklet labels, and carton number. Each carton will also be labeled with inner and outer booklet labels and numbered.

9.12.1 Labeling

The tubes will have a label affixed that meets the applicable regulatory requirements and may include, but is not limited to, the following: subject identifier, IP name, lot number, protocol number, carton number, caution statement, storage, and sponsor identification.

All empty packaging or packaging containing unused tubes should be saved for final disposition by the sponsor or contract pharmacy.

Final labeling will comply with the regulatory requirements of each country where the study will be conducted.

9.12.2 Packaging

Investigational products will be packaged in high-density polyethylene, 35×100 mm tubes weighing 50 g from which a maximum of 36 g of IP can be extracted. Trifarotene cream HE1 and vehicle will be packaged so as to be blinded to the investigator, the study clinic personnel, and the subjects.

10. STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

Subjects who agree to participate in the photography and/or PK substudy must provide written informed consent before photographs or serial blood samples are collected.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

10.1.1 Overall Study Schedule

The planned sequence and maximum duration of the study periods for each subject will be as follows:

1. Screening: up to 97 days. Before asking a subject to enter washout, investigators should confirm the subject meets study eligibility criteria, except for LI severity (inclusion criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined.
2. Double-blind treatment: Twice weekly for 90 days.
3. Optional Open-label Extension treatment: Twice weekly for 90 days.
4. Follow-up: 14 days after last study drug application.

The maximum treatment duration for each subject is approximately 90 days for subjects who choose not to continue into the OLE, and 180 days for those who choose to continue.

The maximum study duration for each subject is approximately 291 days.

10.2. Study Periods and Visits

It is suggested that quality of life assessments be conducted first to avoid any bias, and that the IGA be recorded as the first LI assessment at every visit.

10.2.1 Screening and Washout

10.2.1.1 Screening Visit (Visit 1)

Written informed consent must be obtained before any study-related procedures are performed. Before asking a subject to enter Washout (Section 10.2.1.1.1), investigators should confirm the subject meets study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the

site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined.

The following procedures will be performed during Screening:

1. Obtain written informed consent.
2. Assign a screening number when a subject begins screening.
3. Assess inclusion/exclusion criteria.
4. Collect demographic information.
5. Record medical history, including current therapies (e.g., prescription and nonprescription medications).
6. Perform a physical examination.
7. Measure vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse).
8. Measure height, weight, and calculate body mass index (BMI).
9. Record IGA.
10. Record VIIS.
11. Record roughness assessment.
12. Record palm/sole assessment.
13. Record palm/sole assessment of fissuring.
14. Record ectropion score.
15. Perform a 12-lead ECG.
16. Collect blood and urine for laboratory tests, coagulation panel, and serology.
17. Perform serum pregnancy test for WOCBP.
18. Record concomitant medications.

Procedures for rescreening subjects who initially fail to meet study entry criteria are described in Section 14.3.

10.2.1.1.1 Washout

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and begin to washout the prohibited topical and systemic treatments with designated washout periods, as applicable (Table 9-2). Washout may be up to 90 days, as necessary.

After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and to complete any eligibility requirements. During washout, subjects may continue their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid

functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard-of-care treatments in the eCRF. If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.

10.2.2 Double-blind Treatment Period

Eligible subjects who have washed out prohibited medications will be randomized to double-blind study drug.

10.2.2.1 Baseline Visit (Visit 2, Day 1)

The following procedures will be performed on Day 1 in the study clinic:

1. Review inclusion/exclusion criteria.
2. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
3. Perform a limited physical examination.
4. Record vital signs (blood pressure and pulse).
5. Record concomitant medications and concomitant therapies.
6. Record IGA.
7. Record VIIS.
8. Record roughness assessment.
9. Record palm/sole assessment.
10. Record palm/sole assessment of fissuring.
11. Record ectropion score.
12. At sites where the photographic substudy is conducted, take photographs of subjects who have provided informed consent for the photography.
13. Perform a 12-lead ECG.
14. Perform urine pregnancy test for WOCBP.
15. Collect blood and urine for routine laboratory tests (subject must be fasting; i.e., at least 8 hours) and coagulation panel.
16. Randomize via IWRS.
17. Collect a predose PK blood sample (all subjects).
18. Among subjects who consent to participate in the PK substudy, ensure that PK lines are placed before IP application. The IP will be applied in the clinic at this visit, and samples for PK will be taken at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1.
19. Among subjects in the PK study, perform additional ECGs at times of serial sampling.

20. Clinic staff instructs subject on study drug application, applies initial study drug dose and measures amount used (i.e., study staff will weigh kits (tubes and boxes, but not leaflets) before and after the first application. If the product will be applied at home by someone other than the study subject, it is recommended that this person assist with application at this visit to learn how the IP is applied.
21. Assess and record local tolerance/AEs.
22. Dispense study drug and diaries.
23. Advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that at least 24 hours must have elapsed since IP application before their next visit. Subjects should not to apply IP on visit days until after the visit.

10.2.2.2 Telephone Visit (Day 7)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited), and remind subjects that at least 24 hours must have elapsed since IP application before their next visit. Subjects should not apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.2.3 Visit 3 (Day 14 ±5 days)

The following procedures will be performed on Day 14 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Record IGA.
5. Record VIIS.
6. Record roughness assessment.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring
9. Record ectropion score.
10. Assess local tolerance.
11. Record AEs and review diary.
12. Collect a PK blood sample (all subjects).
13. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.

14. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.
15. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.

10.2.2.4 Visit 4 (Day 30 ±7 days)

The following procedures will be performed on Day 30 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Record IGA.
5. Record VIIS.
6. Record roughness assessment.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring
9. Record ectropion score.
10. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
11. Assess local tolerance.
12. Record AEs and review diary.
16. Perform a 12-lead ECG
17. Perform a urine pregnancy test for WOCBP.
18. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours) and coagulation panel.
19. Collect a PK blood sample (all subjects).
20. Among subjects who consent to participate in the PK substudy, ensure that PK lines are placed before IP application. The IP will be applied in the clinic at this visit, and samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose.
21. Among subjects in the PK study, perform an additional ECGs at times of serial sampling.
22. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
23. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before and after study drug application is prohibited.

Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.

24. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.
25. Provide information about OLE option to study subject.

10.2.2.5 Telephone Visit (Day 45)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited), and remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary. Staff will remind subject about OLE option.

10.2.2.6 Visit 5 (Day 60 ±7 days)

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Perform a urine pregnancy test for WOCBP.
5. Record IGA.
6. Record VIIS.
7. Record roughness assessment.
8. Record palm/sole assessment.
9. Record palm/sole assessment of fissuring
10. Record ectropion score.
11. Assess local tolerance.
12. Record AEs and review diary.
13. Collect a PK blood sample (all subjects).
14. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
15. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before and after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP

application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.

17. Provide information about OLE option.

10.2.2.7 Visit 6 (Day 90 ±7 days) or Early Termination

The following procedures will be performed on Day 90 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
2. Perform a limited physical examination.
3. Record vital signs (blood pressure and pulse).
4. Record concomitant medications and concomitant therapies.
5. Record IGA.
6. Record VIIS.
7. Record roughness assessment.
8. Record palm/sole assessment.
9. Record palm/sole assessment of fissuring.
10. Record ectropion score.
11. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
12. Assess local tolerance.
13. Record AEs and review diary.
14. Perform a 12-lead ECG.
15. Perform a urine pregnancy test for WOCBP.
16. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours) and coagulation panel.
17. Collect a PK blood sample (all subjects).
18. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.

For subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 90 days of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing, PK from Day 90 will be carried over to the OLE and will not be repeated. If the subject chooses to continue into OLE, the following additional procedures will be done:

1. Have the subject sign OLE-specific informed consent.
2. Measure subject's weight.

3. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that at least 24 hours must have elapsed since IP application before the PK draws at the Day 120 and Day 180 Visits, and not to apply IP on visit days until after the visits.
4. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit (only for subjects who choose to continue into the OLE).
5. Dispense study diary.

10.2.3 Follow-up Telephone Call (±14 days after Day 90) – Only Subjects Who Do Not Continue into Open-label Extension

Clinic staff will telephone subjects who choose not to continue into the Open-label Extension within 14 days after Day 90 to assess any ongoing AEs.

10.2.4 Open-label Extension

Subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 90 days of double-blind treatment may choose to continue into an optional 90 day OLE with trifarotene cream HE1 200 µg/g. During the OLE, subjects will return to the site at Days 104, 120, 150, 180 and 194. Additional PK samples will be drawn at Days 120 and 180 from all subjects who continue into the OLE.

10.2.4.1 Telephone Visit (Day 97)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.2 Visit 7 (Day 104 ±5 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.

8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
11. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.
12. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit (Day 120), and if the Day 120 visit day coincides with a treatment day, wait until after the visit is complete to apply IP.

10.2.4.3 Visit 8 (Day 120 ±7 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Perform a 12-lead ECG.
11. Perform a urine pregnancy test for WOCBP.
12. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours) and coagulation panel.
13. Collect a PK blood sample (all subjects)
14. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
15. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited.

10.2.4.4 Telephone Visit (Day 134)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.5 Visit 9 (Day 150 ±7 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Perform a urine pregnancy test for WOCBP.
11. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
12. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.
13. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit (Day 180) and if the Day 180 visit coincides with a treatment day, wait until after the visit is complete to apply IP.

10.2.4.6 Visit 10 (Day 180 ±7 days) or Early Termination

The following procedures will be performed at this study clinic visit:

1. Perform a physical examination.
2. Record vital signs (blood pressure and pulse).
3. Record concomitant medications and concomitant therapies.
4. Record IGA.
5. Record VIIS.
6. Assess roughness.

7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring.
9. Record ectropion score.
10. Assess local tolerance
11. Record AEs and review diary.
12. Perform a 12-lead ECG.
13. Perform a urine pregnancy test for WOCBP.
14. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours) and coagulation panel.
15. Collect a PK blood sample (all subjects)
16. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.

10.2.4.7 Follow-up Evaluation – Open-Label Extension (Day 194 or 14 days after End of Open label Treatment/Visit 11)

At 14 days after the last administration of the IP, the following procedures will be performed:

1. Perform a limited physical examination.
2. Record vital signs (blood pressure and pulse).
3. Record any concomitant medications/therapies.
4. Record IGA.
5. Record VIIS.
6. Assess roughness.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring.
9. Record ectropion score.
10. Assess and record AEs occurring since the last evaluation and review diary.
11. Perform a urine pregnancy test for WOCBP.

10.3. Assessments

The 5-point IGA is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. The IGA scale was developed with the support of experts from academic reference centers for the treatment of ichthyosis. Each level of severity will consider both the severity of scaling and the severity of roughness (Section 10.3.1.2). While retinoid treatment is expected to reduce scale, it may increase erythema; therefore, in this study, erythema will be evaluated as part of local tolerability.

10.3.1 Efficacy Variables

All efficacy measurements will use scales previously used for dermatological studies or as defined in the following sections.

10.3.1.1 Investigator's Global Assessment

The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear and at least a 2-grade change from Baseline at Day 90/EOT in the Double-blind Period on a 5-point IGA full body scale.

The investigator will rate the subject's condition using the 5-point IGA at each time point shown in the Schedule of Events (Section 2.2).

The IGA will be measured on a 5-point scale, excluding the following areas: knees, elbows, neck, palms, soles, axillae, groin, and scalp:

0	Clear	No scaling and no roughness
1	Almost Clear	Occasional fine scales; hardly palpable roughness (mostly smooth)
2	Mild	Small and fine scales predominate; no more than a few large scales; mild roughness on palpation
3	Moderate	Some large scales that may be thick; coarse roughness on palpation
4	Severe	Confluent, primarily large (>1 cm), thick scales with plate-like hyperkeratosis

10.3.1.2 Visual Index for Ichthyosis Severity – Scaling

The secondary endpoint is the number of subjects in each treatment group who experience a severity score of 0 or 1 at Day 90/EOT on the overall 16-point VIIS for scaling.

The investigator will rate the subject's condition using the 5-point VIIS for each body area (chest/abdomen, back, legs, and arms) and an overall score at each time point shown in the Schedule of Events (Section 2.2):

0	Normal skin; no perceptible scale or smoothening
1	Areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings, shininess, waxiness) or small scales (visibly separated/fractured stratum corneum)
2	Confluent smoothening (diminished fine skin markings, shininess, waxiness) or small scales (visibly separated/fractured stratum corneum)
3	Confluent scales (visibly separated/fractured stratum corneum) including some large (>1 cm), thick scales
4	Confluent, primarily large, thick scales

10.3.1.3 Individual Score for Roughness

The amount of roughness of the skin overall will be measured on a 5-point scale.

0	Clear	Smooth skin
1	Almost Clear	Hardly palpable roughness
2	Mild	Mild roughness (fine sand paper-like)
3	Moderate	Moderate, coarse roughness (coarse sand paper-like)
4	Severe	Very coarse skin (broken cornflakes-like)

10.3.1.4 Palm/Sole Assessment

Thickening of the skin on the palms and soles will be measured on a 5-point scale.

0	Clear	No thickening, no roughness, no fissure
1	Almost Clear	Only slight thickening, minimal to no roughness, no fissures
2	Mild	Some thickening, mild roughness on palpation, few fissures may be present
3	Moderate	Substantial and diffuse thickening, coarse roughness on palpation may be present, fissures may be present
4	Severe	Very thickened and rough skin, numerous fissures

10.3.1.5 Palm/Sole Fissuring Assessment

Fissuring will be assessed by recording the presence or absence of fissures, the number of fissures present, and the pain associated with each fissure. A fissure is a longitudinal and deep crack that separates the stratum corneum and may penetrate down to the dermis, causing pain and sometimes bleeding. The subject will assess pain associated with fissures as ranging from 0-3 (none, mild, moderate, severe).

10.3.1.6 Dermatology Life Quality Index

The DLQI is a dermatology-specific Quality of Life instrument. It is a simple 10-question validated questionnaire with 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment); higher scores indicate poorer quality of life. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology.

10.3.1.7 EQ-5D Quality of Life Questionnaire

The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the subject's self-rated health on a vertical 0-100 VAS. This can be used as a quantitative measure of health outcome that reflects the subject's own judgment.

10.3.1.8 Ectropion Severity Score

The ESS has a maximum score of 8 points. A higher score indicates a worse ectropion. The score takes the severity of ectropion in terms of lateral and medial apposition, scleral show, conjunctival show, and roundness of the eye into account and gives an indication of the functional aspects involved in ectropion by scoring redness, excess tear film, and the position of the lacrimal punctum.[14]

Table 10-1: Ectropion Severity Score

	Points per Item		
	0	**0.5**	**1**
Lateral apposition	Nonaffected	—	Affected
Medial apposition	Nonaffected	—	Affected
Scleral show	No	≤1 mm	>1 mm
Conjunctival show	No	—	Yes
Excess tear film	No	—	Yes
Redness of the eye	No	—	Yes
Round canthus	No	—	Yes
Punctum lacrimale	Invisible	Emerging	Visible
Maximum score			8 points

Source: Korteweg SFS, Stenekes MW, van Zyl FE, Werker PMN. Paralytic Ectropion treatment with lateral periosteal flap canthoplasty and introduction of the ectropion severity score. *Plast Reconstr Surg Glob Open.* 2014;2(5):e151.

10.3.1.9 Photography Substudy

All sites that have photographic capability will take photographs as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional photographic informed consent form (ICF).

10.3.2 Clinical Pharmacology

10.3.2.1 Pharmacokinetic Analysis Methods

The pharmacokinetic characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis (NCA).

10.3.2.2 Pharmacokinetic Parameters

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit for trough values.

Subjects who provide written informed consent to participate in the optional PK substudy will provide blood samples for PK analysis predose on Day 1 and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30.

The PK parameter estimates will be completed using WinNonlin (Pharsight Corporation) software using the actual elapsed times from dose administration to sample collection (i.e., not nominal time).

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the maximum concentration (C_{max}) and the time of C_{max} (T_{max}). Additional details of the parameters and their calculation and evaluation will be included in the statistical analysis plan (SAP).

Table 10-2 shows the PK parameters that will be computed for each subject for samples obtained over the planned sampling intervals.

Table 10-2: Pharmacokinetic Parameters

Parameter	Description of Parameter
C_{max}	Maximum (or peak) serum concentration
T_{max}	Time at which C_{max} is observed
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration
$AUC_{(0-inf)}$	Area under the plasma concentration-time curve from time 0 to infinity (if data permit)
$t_{1/2}$	Apparent first order terminal elimination half-life
λ_z	Apparent terminal phase rate constant (if data permit)

10.3.3 Sample Collection

Samples will be collected at the time points specified in the Schedule of Events (Section 2.2). Specimen preparation, handling, shipment, and storage for the complete blood count, chemistry, and urinalysis are described in the study laboratory manual. Finding veins in subjects with this disease can be challenging. Blood draws will be done at the corresponding study visits before application of the IP and should be 24 hours after IP application. Subjects must not apply the IP to the area where blood will be drawn within 24 hours before their next study visit to avoid contamination of the blood by IP that remained in the skin. For subjects in the PK substudy, a cannula should be placed before IP application and the cannula site may be occluded to prevent contamination with IP.

Actual PK sample times for subjects in the PK substudy will be recorded in the eCRF.

Blood

For subjects not in PK substudy:

The expected amount of blood to be drawn at each visit varies from approximately 6 mL to a maximum of 21 mL (Screening Visit only). The total amount of blood drawn for the study will be about 123 mL per subject, unless the subject takes part in the PK substudy.

For subjects in PK substudy:

For subjects who opt to participate in the PK substudy, extra blood samples will be drawn at Visit 2 and at Visit 4 for PK analysis. The amount of blood to be drawn per subject at each of these visits will be approximately 54 mL. For subjects taking part in the substudy, the total amount of blood drawn for the entire study will be approximately 195 mL.

Urine

Urinalysis will be performed at central laboratory. Dipstick and urine pregnancy tests will be conducted on site.

10.3.4 Safety Variables

Safety assessments will include the evaluation of AEs, including local tolerability (stinging/burning, pruritus, and erythema), clinical laboratory assessments, vital signs, 12-lead ECGs, and physical examinations.

10.3.4.1 Clinical Laboratory Safety Assessments

10.3.4.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 2.2).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides
Coagulation Panel:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones
Pregnancy Test:	for women of childbearing potential only; serum at Screening, urine at each other visit.
Serology	Hepatitis B surface antigen, and hepatitis C

All blood samples for the clinical laboratory tests must be taken in a fasting state, at least 8 hours after the previous drug application.

Blood and urine samples for hematology, and serum chemistry will be sent to a central laboratory for analysis. Urine pregnancy tests and dipstick will be conducted at the study sites.

10.3.4.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

Samples for assessment of clinical laboratory tests will be transported to the Clinical Reference Laboratory (see the study laboratory manual for addresses).

10.3.4.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Mayne Pharma LLC prior to beginning the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically significant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical significance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically significant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.4.2 Clinical Examinations

10.3.4.2.1 Vital Signs

Vital signs, including height and weight (only assessed at Screening), blood pressure, and pulse will be measured.

10.3.4.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. All ECG recordings will be identified with the subject number, date, and time of the recording. Gel ECG electrodes may be used for ECGs because they are more conductive and cause less trauma on compromised skin. Efficacy assessments should be conducted before ECGs to avoid possible artefact/changes from the ECG.

For subjects in the PK substudy, additional ECGs will be performed postdose during serial blood sampling on Day 1 and Day 30.

If there is a marked prolongation of the QT/QTc interval during treatment, a subject should be discontinued from the IP but remain in the study until full resolution of the event. The DSMB will be informed immediately of such an occurrence.

10.3.4.2.3 Physical Examination

A complete physical examination excluding the genitourinary examination will be performed at Screening, while limited physical examinations (to include head, eyes, ears, nose, and throat, cardiorespiratory, abdomen, and range of motion) will be performed as indicated in the Schedule of Events (Section 2.2).

10.3.4.2.4 Other Safety Variables

Local tolerability will be assessed on a 0-3 scale (none, mild, moderate, severe). All application site reactions will be recorded as TEAEs in the diary. These should include the date and severity of the TEAE.

10.3.4.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

10.4. Procedural Adjustments Due to COVID-19

The coronavirus disease 2019 (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted to control the spread of the disease. It is recommended that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19.

Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 (Double-blind Period; Table 2-1), Visits 7-11 (OLE Period; Table 2-2) and unscheduled visits may be conducted remotely. Screening and baseline visits must be performed onsite only, and must be postponed or scheduled for when onsite visits can be safely conducted.

Procedural adjustments due to COVID-19 when it is inadvisable or not possible to conduct an onsite study visit are detailed in Appendix B.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in subjects treated with control product are also considered AEs.

11.1.2 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADRs).

The phrase “responses to an investigational product” means that a causal relationship between an investigational product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IP qualify as ADRs.

All AEs for which the judgment of relationship to IP is “possible” or higher will be considered ADRs. If a relationship to IP is not provided, then the AE must be treated as if it were “possible.”

11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For a preapproval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events.

11.1.4 Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first application of IP (trifarotene or vehicle) and not more than 14 days after the last application of IP.

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review by a study monitor.

All reported AEs, including local and systemic AEs not meeting the criteria for SAEs, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All reported AEs occurring while on study must be documented appropriately regardless of relationship. All reported AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of a reported AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study clinic personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 14 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs. In addition, although local tolerability will be assessed on a 0-3 scale, all application site reactions should be recorded as AEs.

The Tolerability Assessments Form at each visit collects a numeric severity score by body area for erythema, stinging/burning, and pruritus.

In addition, if skin irritation is more than the expected erythema, stinging/burning, and pruritus with the application of this topical retinoid (i.e., clinically relevant), please enter the application site reactions in the Adverse Event description section. If a diagnosis is known, record the diagnosis. If a diagnosis is known and there are other signs/symptoms that are not generally part of the main diagnosis, record the diagnosis and each sign/symptom on a separate line. If a diagnosis is not known, record each sign/symptom on a separate line. Examples are allergic contact dermatitis, sunburn, skin erosion, and swelling.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as follows:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3 Action(s) Taken

All AEs will be treated/managed according to standard practice. The following actions may be taken with regard to the IP. Section 9.4 describes dose adjustment and stopping rules for individual subjects.

Action(s) taken may consist of the following:

Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by reducing the frequency of application.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome of an AE at the time of last observation will be classified as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to IP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related	An AE with a reasonable time sequence to administration of the IP, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Related	An AE occurring in a causal plausible time relationship to IP administration that cannot be attributed to a concurrent disease or other drugs, chemicals, or events. The AE relationship to the IP must be assessed separately by the investigator and Mayne Pharma LLC.

11.2.3 Documentation

Any AE that occurs during the Screening Period will be captured as on the AE page of the eCRF (not medical history). All AEs that occur within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP(s)

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject may be withdrawn for treatment but continue to be followed for efficacy and safety in the study. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

It is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

Any AE will be followed (up to a maximum of 14 days after the last dose of IP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to Premier Research within 24 hours of first becoming aware of the event by e.g., completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the Premier Research by one of the following methods:

Email: globalPV-US@premier-research.com

Email: PVDS-ROW@premier-research.com

Fax number: +1 215 972 8765

Fax number: +421 2 6820 3713

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of IP(s)
- Date of last dose of IP(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s) ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, adverse event, date of occurrence, subject identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the Premier Research Pharmacovigilance Department using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB)/independent ethics committee (IEC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.2 Adverse Drug Reactions

All ADRs should be reported by the investigator in the eCRF.

Suspected serious ADRs must be reported to the sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.3 Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported by Premier Research to Mayne Pharma LLC in aggregate monthly status reports.

11.3. Special Considerations

11.3.1 Adverse Events of Special Interest

Since topical retinoids are associated with local application site AEs, particularly when beginning treatment, these events will be followed closely during the study and considered AEs of special interest (AESIs).

11.3.2 Pregnancy

All WOCBP who participate in the study should be counseled on the need to practice highly effective birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during IP treatment will be immediately discontinued from study treatment. The investigator must report the pregnancy of any woman who becomes pregnant during or within 30 days after discontinuing treatment as if it were an SAE within 24 hours of learning of the pregnancy, to Premier Research Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. If a partner

of a male study subject becomes pregnant, the investigator must report the pregnancy as soon as possible after learning of it to the Premier Research Pharmacovigilance using the Pregnancy Data Collection Form. A separate pregnant partner ICF will be required.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy in a study subject. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Pregnancy Data Collection Form and forwarded to Premier Research Pharmacovigilance. The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly. In such case, an additional form (Serious Adverse Event Report Form) must be filled out by the investigator and provided to Premier Research Pharmacovigilance within 24 hours of knowledge of the pregnancy's serious outcome.

Among the clinical studies, 12 pregnancies were reported: 4 resulted in normal births; 5 resulted in spontaneous abortions (none of which was considered related to CD5789); 1 was electively aborted, and 2 were lost to follow-up (IB for CD5789 Cutaneous Formulation).

12. DATA SAFETY MONITORING BOARD

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including LI. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate under a charter that will be finalized prior to the start of the study. The DSMB will meet at least 3 times during the conduct of the study: when the study begins, when 15 subjects have enrolled in Cohort A and have completed at least 28 days of treatment, and after 60 subjects have enrolled in the study.

The DSMB will meet after 15 subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data (including PK and ECG results). The safety data will be unblinded to the DSMB. At that time, the DSMB will decide whether Cohort B may begin enrolling. The DSMB will have the authority to recommend to the sponsor that the study be modified, placed on hold, or stopped if serious safety issues are discovered. The DSMB will provide its input to Mayne Pharma LLC. Any protocol changes the DSMB may suggest will be submitted to all applicable regulatory bodies for review and approval.

In case of significant toxicity, the DSMB may choose to review the available safety data and recommend stopping recruitment in a particular dose group.

Stopping rules for individual subjects are in Section 8.4. The DSMB committee members are as follow:

- Univ. Prof. Dr. med. Steffen Emmert, Director at Clinic and Polyclinic for Dermatology & Venereology University Medical Center Rostock
- Jeffrey Louis Sugarman, MD, PhD Pediatric Dermatologist
- Moise L. Levy, MD, Pediatric Dermatologist
- Gabriele Accetta, PhD, Biostatistician

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. A SAP that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a P value of ≤ 0.05 will be considered statistically significant.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will include the number and percentage of subjects in each category.

The primary analysis period is the first 90 days of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after the database is locked. A second analysis will take place for endpoints assessed from Day 90 through the OLE

Period. The baseline for the safety and efficacy parameters will be measured at Visit 1 or Visit 2, per the Schedule of Events for both the Double-blind Period (Table 2-1) and OLE (Table 2-2).

13.1.1 Analysis Populations

The following 5 analysis populations are planned for the Double-blind Period of this study:

- Safety: all subjects who are randomized to treatment and receive at least 1 application of study drug in the Double-blind Period. This population will be the primary population for analyses of safety.
- Intent-to-treat (ITT): all randomized subjects. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study.
- Modified intent-to-treat (mITT): all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period.
- Per-protocol (PP): subjects in the mITT Population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations.
- Pharmacokinetic: all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. This population will be used to summarize all PK endpoints.

The following analysis populations are planned for the OLE of this study:

- OLE Safety: all subjects who complete the 90-day Double-blind Treatment Period and receive at least 1 application of study drug in the OLE.
- OLE ITT: all subjects who complete the 90-day Double-blind Treatment Period and sign the OLE informed consent.
- OLE mITT: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6.
- OLE PP: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study.

Inclusion in the analysis populations will be determined prior to database lock. Deviations related to COVID-19 will also be evaluated in determining PP population eligibility.

If a subject is randomized incorrectly or is administered the incorrect IP, analyses of the ITT and mITT populations will be based on the assigned treatment whereas all other analyses will be based on the actual treatment received.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

For the Double-blind Period, the numbers of subjects randomized, completing Day 90 of the study, and withdrawing early from the Double-blind Period, along with reasons for withdrawal, will be tabulated overall and by randomized treatment group. The number of subjects in each analysis

population will be reported. The number of subjects completing study milestones will also be tabulated by randomized treatment group. This analysis will be conducted for the ITT population.

For the OLE, the number of subjects entering the OLE, completing the study, and withdrawing early, along with reasons for withdrawal, will be tabulated overall. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated. This analysis will be conducted for the OLE ITT population.

13.1.2.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations promptly. All deviations must be addressed in study source documents, and reported to Premier Research or Mayne Pharma LLC. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

Subjects who taper to once-weekly application or who take a “drug holiday” will not be reported as having deviated from the protocol.

13.1.2.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for the ITT and OLE ITT populations.

Demographic variables will include age, sex, race, ethnicity, height, weight, and BMI. Baseline subject characteristics will include medical history, physical examination findings, and IGA score.

Prior and concomitant medications will be summarized by randomized treatment group, by the number and percentage of subjects taking each medication, and classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of each subject’s dose, and in terms of duration of exposure for each period. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group. Additionally, the number of subjects who are compliant with investigational product will be presented by treatment group for the Double-blind Period and overall for the OLE.

Subjects who taper to once-weekly application or who take a “drug holiday” will not be reported as having deviated from the protocol.

13.1.4 Efficacy Analysis

The ITT population will be used as the primary population for the primary analysis of efficacy at Day 90. Select efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE using the OLE ITT, OLE mITT, and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE.

Efficacy endpoints will be based on investigator assessment.

13.1.4.1 Efficacy Endpoints

Primary efficacy endpoint: The proportion of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 2-grade change from Baseline at Day 90/EOT in the Double-blind Period on the 5-point IGA scale.

Secondary: The secondary endpoints are as follow:

- The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Day 90:
  - 5-point VIIS scale for scaling
  - Individual score for roughness (Scale: 0–4)
  - Palm/sole Assessment (Scale: 0–4)
  - Quality of life per DLQI
- The difference in proportion of subjects with presence of fissures on palm/soles (presence/absence, number of fissures, and pain associated with fissures [on a 0-3 scale]) at Day 90 between the active trifarotene cream HE1 and vehicle groups

Exploratory: The exploratory endpoints are as follow:

- The difference in mean ectropion scores (ESS of 0–8) between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90
- The difference in quality of life per EQ-5D-5L scores between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90

13.1.4.2 Primary Analysis

For the Double-blind Period only, the number and proportion of subjects in each treatment group with successful resolution of LI by Day 90/EOT will be presented. The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group, 95% CIs for the differences, and P-values for the differences in treatment will also be presented.

Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from baseline will be provided for IGA scores for both periods.

13.1.4.3 Secondary Analyses

Secondary and exploratory efficacy endpoints will be analyzed separately for each period (Double-blind and OLE) using descriptive statistics.

Additionally, for the Double-blind Period only, change from Baseline in continuous secondary endpoints through Day 90 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate.

For subjects who report having fissures, descriptive summaries of the number of fissures and pain related to fissures will also be presented by treatment group and body area for each period.

The DLQI scores will also be analyzed using descriptive statistics through Day 90.

The proportion of subjects with at least a 50% reduction in IGA score from Baseline will be analyzed using the same logistic regression analysis described in Section 13.1.4.2.

13.1.4.4 Exploratory Analyses

Descriptive summaries and the changes from baseline will be provided for ectropion scores and EQ-5D-5L scores by visit for each period. No formal inferential analyses will be conducted for exploratory endpoints.

13.1.4.5 Corroborative, Sensitivity, and Other Analyses

To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using multiple imputation (MI) for the Double-blind Period only. Multiple-imputations will be used to replace missing IGA outcomes using multiple draws from the posterior predictive distribution estimated from the treatment groups. IGA scores will be imputed and then categorized as treatment success according to Section 13.1.4.1. Imputation will not be performed for the OLE. Full details will be specified in the SAP.

Thorough assessment on the extent of missing data and procedural adjustments due to COVID-19 as it pertains to the primary and secondary efficacy endpoints will be conducted ahead of database lock, and additional sensitivity analyses may be performed. Full details will be documented in the SAP.

The proportion of subjects who experience a 2-grade change from baseline to Day 90 in individual score for roughness and palm/sole assessment will also be explored using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group and the 95% CIs for the differences will be presented.

For analyses involving study site, if the number of subjects per site is small, sites may be pooled for safety and efficacy analysis or omitted from statistical models as the anticipated number of subjects per site is small, treatment is self-administered, and the sites are using standardized procedures for all assessments. If the distribution of enrollments at sites is such that one or few are

enrolling a majority of subjects, a subgroup analysis by site may be performed. The final determination will be made prior to database lock.

Details of these analyses will be further detailed in the SAP.

13.1.5 Clinical Pharmacology Analyses

13.1.5.1 Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics. Descriptive statistics reported will include the arithmetic mean, SD, CV%, geometric mean, minimum, maximum, and median. Only the range and the median will be reported for T_{max}, as this is a categorical parameter. The PK parameters will also be summarized by treatment using descriptive statistics.

Individual plasma concentration plots and mean data graphs will be produced using both linear and semi-logarithmic scales. Mean data graphs will show plasma concentration profiles by treatment group.

Pharmacokinetic plasma parameter estimates and summaries will be completed for the subjects in the PK population. Testing of PK parameters will be outlined in the SAP.

13.1.6 Safety and Tolerability Analyses

Safety analyses through Day 90 of the Double-blind Period will be conducted using data from the Safety Population and safety analyses in the OLE will be conducted using the OLE Safety Population (as defined in Section 13.1.1). Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, and physical examination results. No formal inferential analyses will be conducted for safety variables in either period.

13.1.6.1 Local Tolerability

During all clinic visits, the investigator will assess local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]) for each treated body area (chest/abdomen, back, arms, legs, and face/neck). Descriptive summaries will be presented by period, treatment group, and visit.

13.1.6.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1 or higher.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first, or
- AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first.

The number and percentage of subjects with AEs will be displayed by each treatment group in the Double-blind Period and overall in the OLE by system organ class and preferred term. Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.6.3 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each treatment group at each time point in each period.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory parameter by treatment group and by study visit in each period.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.1.6.4 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse for each period.

The number of subjects with vital signs values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each parameter by period, by treatment group and by study visit. Pre- and post-treatment values may also be presented with an analysis of mean changes from baseline.

13.1.6.5 Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point in each period. Abnormal results will be grouped as clinically significant and not clinically significant.

A comparison of QT results will be presented. Summary statistics will be displayed by period, by treatment group, and by visit for QT and the QT interval corrected for heart rate (QTc) calculated using Fridericia's QT correction methods.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTcF interval (Fredericia's correction methods), and HR for each treatment group at each time point in each period.

13.1.6.6 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group in each period.

13.1.7 Interim Analysis

No interim analyses are planned.

13.2. Sample Size Determination

Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively. This study is not powered to detect a difference between the 2 active arms.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Mayne Pharma LLC agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with ICH GCP, and the applicable United States (US) Code of Federal Regulations (CFR). The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IP(s), and their specific duties within the context of the study. Investigators are responsible for providing Mayne Pharma LLC with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all

documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Premier Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Premier Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Premier Research

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory/GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening Visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4. Study Documents

All documentation and material provided by Mayne Pharma LLC for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The informed consent forms are submitted with this protocol.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent forms and ask questions before signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory/Good Clinical Practice Documents

The regulatory/GCP documents are listed below.

- Signed original protocol (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and subinvestigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form Signature Log/Delegation of Study-related Duties
- Approved ICF and subject materials
- FDA1572 and financial disclosure forms, as applicable (US sites)
- Any other relevant GCP documents

The regulatory/GCP documents must be received from the investigator and reviewed and approved by Mayne Pharma LLC or its designee before the study site can initiate the study and before Mayne Pharma LLC will authorize shipment of IP to the study site. Copies of the investigator's regulatory/GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the trifarotene (CD5789) Cream IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and IP accountability records should also be retained as part of the investigator's regulatory/GCP documents. It is the investigator's responsibility to ensure that

copies of all required regulatory/GCP documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.5. Data Quality Control

Mayne Pharma LLC and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

Mayne Pharma LLC and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Mayne Pharma LLC personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures

- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF will be provided to the sites. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Mayne Pharma LLC or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan (CMP).

14.5.2 Data Management

Mayne Pharma LLC or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data management plan (DMP) will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries will be provided to the sites.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Mayne Pharma LLC or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or clinical study report [CSR])

Mayne Pharma LLC or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Mayne Pharma LLC immediately.

14.6. Study Termination

The study may be terminated at Mayne Pharma LLC's discretion at any time and for any reason.

The DSMB may recommend discontinuation of the study if they find evidence of unacceptable risk to subjects.

14.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, Mayne Pharma LLC or designee will notify the IECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

14.6.2 Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by Mayne Pharma LLC, IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Mayne Pharma LLC or its designee will notify the IECs and regulatory authorities about the premature termination as required according to national laws and regulations. Mayne Pharma LLC or its designee must clearly explain the reasons for premature termination.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the IND or IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is terminated prematurely, all investigators have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Follow-up Visit.

The study might resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or FDA.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. Mayne Pharma LLC may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1 Record Retention

For sites in the US, the investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until 1 of the following occurs:

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

Outside of the US, after completing the study, Mayne Pharma LLC will receive the original eCRFs or at least a legible copy and retain the documents for at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

14.7.2 Sample Retention

Blood samples will be used for purposes related to this study only, and will not be stored for future research. The samples will be stored until they are no longer needed, and the decision has been

made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

Data collected for this study will be analyzed and stored at Premier Research.

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Mayne Pharma LLC. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9. Use of Information and Publication

All information concerning trifarotene (CD5789) cream HE1, Mayne Pharma LLC's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Mayne Pharma LLC or its designee to the investigator, and not previously published, is considered confidential and remains the sole property of Mayne Pharma LLC. Case report forms also remain the property of Mayne Pharma LLC. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by Mayne Pharma LLC in connection with the continued development of trifarotene (CD5789) cream HE1 and thus, may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Mayne Pharma LLC. Publication or other public presentation of trifarotene (CD5789) cream HE1 data resulting from this study requires prior review and written approval of Mayne Pharma LLC. Abstracts, manuscripts, and presentation materials should be provided to Mayne Pharma LLC for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until Mayne Pharma LLC has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

15. FINAL CLINICAL STUDY REPORT

Mayne Pharma LLC will retain ownership of the data.

The final CSR will be written within 1 year of completion of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

16.2. Subject Information and Informed Consent

A properly constituted, valid IRB or IEC must review and approve the protocol, the investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed consent prior to enrollment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Mayne Pharma LLC, and/or the sponsor's designee. Collection of informed consent has to be documented in the eCRF.

Furthermore, the subject will be informed that if he or she wishes to drop out or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

16.3. Approval by Institutional Review Board and Independent Ethics Committee

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's or the sponsor's representative before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must follow local country requirements.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by Mayne Pharma LLC before implementation.

16.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

17. REFERENCES

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3. Vahlquist A, Gånemo A, Virtanen M. Congenital ichthyosis: an overview of current and emerging therapies. *Acta Derm Venereol.* 2008;88(1):4–14.
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12. Chiaretti A, Wismayer DS, Tortorolo L, Piastra M, Polidori G. Salicylate intoxication using a skin ointment. *Acta Paediatr*. 1997;86(3):330-331.
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18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER:	18-ICH-001
PROTOCOL TITLE:	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 90-day, Safety, Efficacy, and Systemic Exposure Study followed by a 90-day Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
FINAL PROTOCOL DATE:	v4.0 for Ukraine, 19-Nov-2020

The undersigned acknowledges possession of and has read the product information (e.g., investigator's brochure) on the IP and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected subjects in his/her care, according to the study protocol.

He or she agrees to use the study material, including IP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Mayne Pharma LLC.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Mayne Pharma LLC within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IP.

He or she agrees to comply with Mayne Pharma LLC and regulatory requirements for the monitoring and auditing of this study. In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

APPENDICES

A. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives (and applicable regulations/guidances):

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents>

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

B. Procedural Adjustments Due to COVID-19

The coronavirus disease 2019 (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted to control the spread of the disease. It is recommended that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19.

Trifarotene cream HE1 does not increase the risk for contracting COVID-19.

Although it is preferable to conduct all necessary study assessments in person (onsite visits), it may not be possible as a result of COVID-19-related travel restrictions, site closures, or subject confinement. If the subject becomes infected with COVID-19, the investigator or the treating physician will decide on continuation of the study treatment; note that topical trifarotene does not modify immunity.

The skin of individuals with LI is thick, scaly, and often dry, tight, and inelastic. This rigidity may produce major discomfort through formation of painful cracks in the skin and open areas. Extreme thickening of the skin on the soles of the feet can make walking difficult for many patients, and cracks and fissures on the fingers can make even simple tasks difficult or painful. Tight skin can interfere with joint mobility, and over time, lead to decreased joint mobility. Some individuals may be unable to close their eyes completely (ectropion) because of the tightness of the skin around the eyes and eyelids and may seem to "sleep with their eyes open." In addition, the general aspect of this chronic and difficult to manage skin disease often causes depression. For these reasons, as well as the lack of treatment options for individuals with LI, Mayne Pharma thinks it is important for this patient population to continue having access to the treatment offered in this study.

The best way to ensure the reliability of the data collected is to follow the Study Protocol. However, the subjects' safety and wellbeing is a top priority. Therefore, in extraordinary situations when it is inadvisable or not possible to conduct an onsite study visit, please follow these procedures.

❑ **Subject visits:**

Visits 3 to 6 of the Double-blind Period, Visits 7 to 11 of the OLE Period, and unscheduled visits may be conducted remotely (i.e., via telephone or video call). Screening and Baseline Visits must be performed onsite only and must be postponed or scheduled for when onsite visits can be safely conducted. The schedule of telephone visits will continue as indicated in the study protocol (Table 2-1 and Table 2-2); however, onsite visits will be postponed or rescheduled as possible.

When it is not possible to postpone or reschedule the onsite visit, and to ensure the safety of the subjects and to not jeopardize the study procedures and the scientific value of the trial, onsite visits will be changed into telephone visits. As soon as the COVID-19 situation that triggered the use of these procedural adjustments is resolved, the schedule of onsite visits will resume. Information collected during the telephone visits will focus on safety data and primary objective endpoints. The following information is expected to be collected by the investigator/study staff during the telephone visits, as applicable per protocol:

- Ask/remind the subject about any required study procedure considered necessary and according to the protocol. For example:
  - Ask the subject about study drug application
  - Remind the subject to complete the subject diary

  - Advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days
- Record concomitant medications and concomitant therapies
- Record adverse events and information reported in the subject diary
- Record the subject's general health status
- Assess local tolerance at the application sites
- For efficacy assessments, use videoconference for precise scoring; if this is not possible, ask subject if status is the better, worse, or unchanged for the following assessments and enter the outcome for reference in the source data:
  - Investigator's Global Assessment (IGA)
  - Visual Index for Ichthyosis Severity (VIIS)
  - Roughness
  - Palm/sole
  - Palm/sole fissuring
  - Ectropion
- Record urine pregnancy test result for female subjects
- Evaluate treatment compliance, including frequency of application and check if there is cream left in the tubes after application and approximately how much in conjunction with the subject's diary
- Adjust the treatment if necessary, as per study protocol, according to application site tolerance and treatment compliance

Remote visits are not possible in the following instances:

- Baseline visits will be canceled if the subject is unable to go to the site. If this occurs, rescreening may be necessary when the COVID-19 outbreak is resolved.
- End-of-Treatment visits are recommended to occur onsite. Therefore, the telephone visit will be completed, followed by an onsite visit when the COVID-19 outbreak is resolved.

❑ **Pregnancy Tests**

Retinoids are potentially teratogenic and, therefore, monthly pregnancy tests for women of childbearing potential (WOCBP) are considered critical for subject safety. Consequently, urine pregnancy tests, along with the instructions on how to use them, will be sent to the subject's home. The study staff will instruct the subjects how to properly perform the test during the telephone visits and will document it and the result.

❑ **Supply of Study Medication**

All randomized subjects who have already attended the Baseline Visit (Day 1) and have had study staff apply the first administration of the study drug in the clinic and instructed the subject, should continue their treatments to ensure the reliability of the study data and the scientific value of the trial. Therefore, if the subject is not able to travel to the site, the site will ship the study drug and diary to the subject's home using either powers of the study site or an independent distributor contracted by the sponsor, Mayne Pharma LLC or their designee CRO, who will collect the IP at

the site and will ship it to the patient's home ensuring temperature control and confidentiality. Patient diaries may be sent to subjects electronically or via postal service. Completed diaries may be returned to the site in the same manner.

Investigators/site staff will properly record that the subject has been told their study medication will be sent to their home, and when the study medication was received (to be confirmed with the subject using telephone or via e-mail). Subjects should retain any unused IP and return them to the study site at the next onsite visit, when the study staff will weigh the kits (tubes and boxes, but not leaflets).

- **Quality of Life per Dermatology Life Quality Index (DLQI) and EQ-5D Quality of Life Questionnaire**

Quality of Life questionnaires should be completed on the day of the remote visit and prior to applying treatment (if the remote visit falls on a treatment day). Questionnaires may be sent to subjects electronically or via postal service, and completed questionnaires may be returned to the site in the same manner. If subjects are unable to send completed questionnaires to the site, investigators should ask and record the subject's responses during the remote visit.

However, questions relative to social interaction might not be relevant due to social distancing and/or quarantining. This will be captured in the questionnaires and can be differentiated in the analysis.

- **Monitoring visits:**

If onsite monitoring visits are not possible as a consequence of COVID-19 outbreak, remote visits (via telephone) will be arranged in agreement with the study sites to assist the study progression and to ensure study compliance, without reducing the level of monitoring.

- **Participant Information**

Participating subjects must be promptly informed about changes in the study conduct during COVID-19 outbreak. Information about the changes should first be communicated to subjects via a telephone conversation.

In addition, a Subject Information Sheet and Consent Form have been created to tell subjects about how the above-mentioned changes might impact their usual participation in the study. The investigators/study staff will send the information sheet and consent form to the subject by the appropriate means (for example, via email, regular mail, or courier). Investigators/study staff will confirm and document in the medical history the date the patient was informed via telephone and the date the Subject Information Sheet and Consent form were mailed to and received by the subjects, and that the subject provides verbal consent.

- **Informed consent and/or assent process recommendations**

Where country regulation requires that the COVID-19 Information Sheet is signed by the subjects to express their consent to the changes in the study procedures due to COVID-19 or a subject is completing the double-blind part of the study and needs to consent to continue in the open label extension part, the process will be as follows:

1) First option is to collect face-to-face written consent with the investigator according to ICH E6 (R2) and local regulation.
2) When face-to-face written consent is not possible, trial participants can be contacted via phone or video call to obtain remote consents as follows:

a. Informed consent document/assent, if applicable, is emailed, faxed, or sent via courier or regular mail by site staff to subject prior to remote visit.
   - If document is emailed, subject should print document prior to visit.

b. Subject will be contacted via phone or video call by the investigator/designee. Informed consent/assent discussion with the subject will be facilitated by the Investigator or staff delegated to perform this task.
   - Investigator/designee will document details of the remote informed consent process in the trial participant's medical records.

c. Subject will sign and date informed consent/assent while on phone or video call with investigator/designee.
   - During the call or video call, the subject should provide verbal consent and supplement it with an e-mail confirmation
   - Investigator/designee will document the time and date that they witness the signing of the informed consent/assent via phone or video call in the trial participant's medical records.

d. Investigator/designee will sign and date copy of the informed consent/assent documenting that they witnessed the verbal consent of the subject via phone or video call

e. When subject returns to the site, subject will bring the signed consent form (if possible) and will give consent again face-to-face with site staff according to ICH E6 (R2) and local requirements.

f. Investigator/designee will attach the subject signed informed consent/assent to the copy signed and dated by investigator/designee upon receipt.

PROTOCOL/CLINICAL INVESTIGATION PLAN AMENDMENT

PRODUCT NAME/NUMBER:	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER:	18-ICH-001
IND NUMBER:	140538
NCT NUMBER:	NCT03738800
EUDRACT NUMBER:	2018-003272-12
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 90-Day, Safety, Efficacy, and Systemic Exposure Study followed by a 90-Day Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale
PROTOCOL DATE:	Original: 28-Nov-2018
AMENDMENT 1 DATE:	Final v2.0, 10-Jul-2019
AMENDMENT 2 DATE:	Final v3.0 28-Oct-2020
COORDINATING/PRINCIPAL INVESTIGATOR:	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine, PO Box 208059 333 Cedar Street New Haven, CT 06520, USA +1 203 789 1249
SPONSORED BY:	Mayne Pharma LLC 1240 Sugg Parkway Greenville, NC 27834, USA +1 984 242 1400
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive, Suite 150 Durham, NC 27709, USA +1 919 627 9100

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: 18-ICH-001

PROTOCOL TITLE: A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 90-Day, Safety, Efficacy, and Systemic Exposure Study followed by a 90-Day Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale

I, the undersigned, have read this protocol and confirm that to the best of my knowledge, it accurately describes the planned conduct of the study.

SIGNATURE	DATE:
DocuSigned by: Phoevos Hughes Signer Name: Phoevos Hughes Signing Reason: I approve this document Signing Time: 30-Oct-2020 | 10:59:35 PDT 2D1DC1CA65A848718371307AF875E4CE Phoevos Hughes, JD Head of Medical and Clinical Affairs Mayne Pharma LLC	30-Oct-2020 | 10:59:39 PDT
DocuSigned by: Marlis Sarkany Signer Name: Marlis Sarkany Signing Reason: I have reviewed this document Signing Time: 30-Oct-2020 | 10:27:37 EDT 16E[illegible]C1FD466E26F Marlis Sarkany, MD Senior Medical Director Premier Research	30-Oct-2020 | 10:27:46 EDT
DocuSigned by: Adrienne Kuxhausen Signer Name: Adrienne Kuxhausen Signing Reason: I approve this document Signing Time: 30-Oct-2020 | 10:24:18 EDT E5EB[illegible]6B8D5A7D662CF Adrienne Kuxhausen, MS Senior Biostatistician Premier Research	30-Oct-2020 | 10:24:26 EDT

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER	18-ICH-001
EUDRACT NUMBER	2018-003272-12
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 90-Day, Safety, and Efficacy, and Systemic Exposure Study followed by a 90-Day Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale
INDICATION	Lamellar ichthyosis
OBJECTIVES	Primary: To compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in adults and adolescents with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 90 days of treatment. Secondary: • To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% body surface area (BSA) twice weekly. • To assess safety for up to 180 days of dosing with trifarotene cream HE1 200 µg/g.
STUDY DESIGN	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Investigator's Global Assessment [IGA] where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe). Adults and adolescents will be randomized in a double-blind fashion to 1 of 2 doses of trifarotene cream HE1 or vehicle and treated twice weekly for 90 days. Subjects who complete the randomized, Double-blind Period of the study will be eligible to enter a 90-Day, Open-label Extension (OLE) in which additional PK, safety, and efficacy data will be collected. The first cohort of subjects (Cohort A) will randomize adults (≥18 years old) in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle. After the initial 15 subjects complete at least 28 days of treatment, an independent data safety monitoring board (DSMB) will review aggregate safety and tolerability data (including PK and electrocardiogram [ECG] data). If no safety issues are identified, adolescents (ages 12 to 17 years, inclusive) will be allowed to enroll together with adults in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for 90 days in the same manner as subjects in Cohort A. Cohort A will continue enrolling only adult subjects until the DSMB considers it safe to open recruitment in Cohort B. All subjects (Cohort A and Cohort B) who complete the 90-day Double-blind Treatment Period will be eligible to enroll in the 90-day OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for 90 days. Written informed consent will be obtained from a parent/legal guardian for any minor and minors will provide assent before any study-related procedures are performed. Upon signing informed consent and entering the Screening Period, subjects may begin a Washout Period of 90 days. Participants will stop using physical and medical

treatments for LI, including balneotherapy, as well as the following prohibited medications, as applicable. The following list applies to both prescription and over-the-counter medications:

a. Topical treatments

Medication	Washout
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogs	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	2 weeks

b. Systemic treatments

Medication	Washout
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones unless the dose is stable and thyroid-stimulating hormone (TSH) is normal, cytotoxics, bisphosphonates, selective estrogen receptor modulators (SERM), teriparatide, calcitonins, tetracyclines, quinolones, thiazides, long-term use of salicylates, heparin, theophylline, barbiturates, colchicines. Vitamin D analogs taken at stable dose for at least 30 days are allowed.	8 weeks
QT-prolonging drugs	5 half lives
CYP enzyme inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (including, but not limited to the following: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives
Monoclonal antibodies	5 half lives

Before asking a subject to washout of their prescription and over-the-counter prohibited treatments, investigators should confirm the subject meets all study eligibility criteria except for LI severity (inclusion criterion #3). After completing the necessary washout period, subjects will return to the site to have their LI severity assessed and to complete study eligibility requirements.

During washout, subjects may continue their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard of care treatments in the electronic case report form (eCRF). If the standard of care treatments of the face

	and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower but not bathe or swim during the Screening Period. Study drug will be packaged in 50-g tubes from which up to 36 g of investigational product (IP) may be dispensed per application, i.e., the maximum dose per application. Study staff will choose 1 tube from the kit dispensed to the subject at that visit, and apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements; they will weigh the study tube before and after application to determine the amount used. If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied. The kit dispensed at baseline must be weighed before the first tube is chosen for application by the study staff. Weight of the kits dispensed and returned by the subject during the study includes both tubes and cartons, but not leaflets, which need to be removed before weighing. The subject must be reminded to return the kits with tubes and cartons, whether used or not, when returning to the next visit. Thereafter, each subject will apply up to 36 g of study drug as for the first dose on up to 90% of BSA twice weekly 3 to 4 days apart, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of product in a tube. Subjects will record the date and time of study treatment administration in the subject diary. The study protocol limits application of IP to 36 g maximum; no additional tubes can be given, whether during the randomization period or the OLE period. If the study staff and subject note that there is insufficient volume for full body application, the subject should apply trifarotene cream sparingly twice weekly to the most affected areas, and always to the same skin areas. Study cream should be very sparingly applied. Trifarotene cream 100 or 200 µg/g, is a highly potent topical retinoid and it is not necessary to apply much for efficacy; application of more will increase the risk of irritation and systemic penetration. Local tolerability may differ in subjects with LI compared to healthy subjects, as their skin is drier and may be more sensitive. Local tolerability will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45 in the Double-blind Period; at Day 97 and 134 in the OLE) to assess safety; an unscheduled clinic visit may be performed, if necessary. If the treatment causes application site reactions, the frequency of application will be reduced or interrupted only on the area of concern, as indicated herein. During all clinic visits, the investigator will assess local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]) for each body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed: - If a score of 2 (moderate) is recorded for any of the local tolerability assessment scales (stinging/burning, pruritus or erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas. - If a score of 3 (severe) is recorded for any of the local tolerability assessment scales (stinging/burning, pruritus or erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., “drug

	holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas. Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and adverse events (AEs). Any changes in dosing must be documented in the subject diary and the electronic case report form. All subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]) and any AEs, including application site reactions and concomitant medications used. Subjects will also be advised on permitted emollient(s) use on nontreatment days during the study; use of emollient(s) and/or sunscreen(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. At all sites with photographic capability, photographs will be taken as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional photographic informed consent form (ICF). Samples for pharmacokinetic (PK) analysis will be drawn from all subjects at Baseline and at each clinic visit. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained on the skin after the last application. Subjects should not apply IP on visit days until after the visit. In addition, a PK substudy will be conducted on Days 1 and 30 at sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 30 subjects, 15 adults and 15 adolescents. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for these subjects at each of the other clinic visits. For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30. Subjects who complete the Double-blind Treatment Period will have the option to continue into the OLE to assess safety for an additional 90 days with trifarotene cream HE1 200 µg/g twice weekly, on up to 90% of BSA, sparing the scalp, inguinal, and axillary areas. During the study, subjects with heavy facial hair should not apply IP to hair-bearing areas. During the OLE, subjects will return to the site at Days 104, 120, 150, 180, and 194 for safety, tolerability, and efficacy assessments. Blood samples will be drawn for clinical laboratory safety tests and PK at Days 120 and 180. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 97 and Day 134) to assess safety; an unscheduled clinic visit may be performed, if necessary. The coronavirus disease 2019 (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted in order to control the spread of the disease. It is recommended that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19. Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19 -related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 (Double-blind Period; Table 2-1), Visits 7-11 (OLE Period; Table 2-2) and unscheduled visits may be conducted remotely. Screening and Baseline Visits must be performed on site only.

	These visits must be postponed or scheduled for when onsite visits can be safely conducted. The following assessments may occur remotely: • Safety Assessments o Concomitant medications and concomitant therapies. o Adverse Events and related information reported by the patient in the diary o General health status of the patient • Tolerability Assessments • Pregnancy Tests: Urine pregnancy tests along with the instructions on proper use will be sent to the subject's home for women of childbearing potential (WOCBP). Study staff will instruct patient to perform the urine pregnancy at the applicable remote visit. • Study Medication Supply: As necessary and according to applicable local regulations, study medication will be sent to subjects. • DLQI and EQ-5D Questionnaires: Quality of Life questionnaires should be completed on the day of the remote visit and prior to applying treatment (if the remote visit falls on a treatment day). Questionnaires may be sent to subjects electronically or via postal service, and completed questionnaires may be returned to the site in the same manner. If subjects are unable to send completed questionnaires to the site, investigators should ask and record the subject's responses during the remote visit. • Patient Diary: Patient diaries may be sent to subjects electronically or via postal service. Completed diaries may be returned to the site in the same manner.
PLANNED NUMBER OF SUBJECTS	Approximately 120 total subjects; 15 adult subjects in Cohort A and 105 adult and adolescent subjects in Cohort B.
STUDY ENTRY CRITERIA	Inclusion criteria: 1. For Cohort A: subject is ≥18 years old; for Cohort B: subject is ≥12 years old. 2. Subject has known diagnosis of LI. 3. Subject has moderate to severe (IGA 3-4) LI on the IGA of LI severity. 4. Subject has signed an ICF at Screening before any investigational procedures. Subjects <18 years of age (or Age of Majority) must sign an assent form in conjunction with an ICF signed by the parent/legal representative. 5. Subject who is participating in photography has signed a photography ICF. 6. Subject who is participating in the optional PK substudy has signed a PK ICF. Minors, in the event of their reaching majority during the study, should be capable of giving consent to take part in the PK substudy. 7. Subject is not of childbearing potential, who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason), or has documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry. OR Subject is a woman of childbearing potential (WOCBP), i.e. a female ≥12 years of age (regardless of whether they have experienced/reported menarche), or a

male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception:

- bilateral tubal ligation
- combined oral contraceptives (estrogens and progesterone), vaginal ring, or implanted or injectable hormonal contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation
- intrauterine device (IUD) inserted at least 30 days before Baseline

OR

Agrees to abstain from heterosexual intercourse during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

AND

Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application.

Note: Female subjects who are premenstrual at screening should nonetheless follow the pregnancy testing schedule for WOCBP even if they abstain from sexual intercourse while in the study and for at least 1 month after the last study drug application.

8. Women of childbearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine).
9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent/assent, as applicable.
10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

Exclusion criteria:

1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization, including syndromic ichthyoses.
2. Subject has current moderate or severe stinging/burning at Screening.
3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments.
4. Subject with fasting triglycerides >200 mg/dL or >2.25 mmol/L and/or total cholesterol >250 mg/dL or >6.5 mmol/L. Subjects whose triglycerides and/or total cholesterol are within normal limits with a stable dose of lipid-lowering agents for at least 6 months may be included.
5. Subject was previously treated with trifarotene/CD5789 in an acne or ichthyosis study.

	6. Subject has any other significant concomitant disease, or poorly controlled medical condition other than LI that in the investigator's opinion may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis). Subjects with hypothyroidism who are on a stable dose of thyroid hormone replacement therapy and whose TSH is normal may be included. 8. Subject is being treated for major depression disorder and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts. 9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening. 10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal (ULN) defined by the laboratory b. Total bilirubin >1.25 × ULN at Screening. Subjects with known Gilbert's syndrome may be included with total bilirubin >1.25 × ULN c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women d. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L 11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 12. Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment. 13. Subject has a history of long QT syndrome or has clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, or QTcF interval >450 ms. 14. Subject has a known allergy or sensitivity to any of the components of the investigational products. 15. Subject has been exposed to excessive ultraviolet (UV) radiations on the treated zones within 1 month before Baseline visit or is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.). 16. Subject is inherently sensitive to sunlight. 17. Subject is unable or unwilling to stop use of topical or systemic retinoids. 18. Subject is presumed to be abusing drugs or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms. 19. Subject is participating in another interventional clinical trial. 20. Subject is institutionalized. 21. Subject is in any way related to the sponsor, investigator, or site personnel.

INVESTIGATIONAL PRODUCT	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: Up to 36 g per dose of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Extension dose, route, frequency: Up to 36 g per dose of 200 µg/g applied topically twice weekly on up to 90% BSA
REFERENCE PRODUCT(S)	Name: Vehicle cream Double-blind Period dose, route, frequency: Up to 36 g per doseapplied topically twice weekly on up to 90% BSA
TREATMENT REGIMENS	Topical application twice weekly to all affected skin except the scalp, axillae, and inguinal area.
COORDINATING/ PRINCIPAL INVESTIGATOR	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine New Haven, CT 06520, USA
PLANNED STUDY SITES	Approximately 40 sites across North America, Europe, Israel, and Australia

CRITERIA FOR EVALUATION	Primary efficacy endpoint: The proportion of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear on treated areas and at least a 2-grade change from Baseline at Day 90/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA full body scale.
	
	Secondary endpoints:
	
	– The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Day 90:
	  – 5-point Visual Index for Ichthyosis Severity (VIIS) for scaling (overall 16 points for scaling, i.e. 0-4 points for 4 body areas: chest/abdomen, back, arms and legs)
	  – Individual score for roughness (Scale: 0–4)
	  – Palm/sole Assessment (Scale: 0–4)
	  – Quality of life per Dermatology Life Quality Index (DLQI) and children's DLQI (cDLQI)
	– The difference in proportion of subjects with presence of fissures on palms/soles (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) at Day 90 between the active trifarotene cream HE1 and vehicle groups
	
	Exploratory endpoints:
	
	– The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90
	– The difference in quality of life per EQ-5D-5L and EQ-5D-Y score between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90
	
	Safety endpoints:
	
	– Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs
	– Local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]) for each body area (chest/abdomen, back, legs, arms, and face/neck).
	
	Pharmacokinetic endpoints: Plasma concentrations of CD5789 and its major metabolites will be measured.

STATISTICAL METHODS	Analysis Populations: The following are planned for the Double-blind Period of the study: The Safety population will be the primary population for analyses of safety and tolerability and will comprise all subjects who are randomized to treatment and receive at least 1 application of study drug. The intent-to-treat (ITT) population will comprise all randomized subjects. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The modified intent-to-treat (mITT) population comprises all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind

	Period. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The Per-protocol (PP) Population will be defined prior to database lock and will comprise subjects in the mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations. The PK Population includes all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. The PK population will be used to summarize all PK endpoints. The following populations are planned for the OLE of this study: The OLE Safety Population: all subjects who complete the 90-day Double-blind Treatment Period and receive at least 1 application of study drug in the OLE. OLE ITT Population: all subjects who complete the 90-day Double-blind Period and who sign the OLE informed consent. The OLE mITT Population: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6. The OLE PP Population: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study. Subject Characteristics and Disposition: Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and baseline characteristics for all enrolled subjects. Medical history, physical examination findings, and vital sign measurements for all randomized subjects will be presented in listings. Efficacy Analyses: The number and proportion of subjects in each treatment group with successful resolution of LI by Day 90/EOT in the Double-blind Period will be presented. The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream groups, 95% CIs for the differences, and P-values for the differences in treatment will also be presented. The IGA scores as well as secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Day 180 (end of OLE treatment period). Change from Baseline through Day 90 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from Baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and Baseline score value as a covariate. Frequencies of results and 95% confidence intervals will also be reported, and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test. For subjects who report having fissures, the number of fissures and pain related to fissures will also be presented on a scale of 0-3 (none, mild, moderate, severe). Clinical Pharmacology Analyses: Noncompartmental PK analysis will be performed for the PK subset of subjects, as data permit. Plasma concentrations of CD5789 and its major metabolites will be measured and will be listed by subject. Safety Analyses: Safety and tolerability will be assessed based on the incidence of reported TEAEs, and SAEs, including relationship to study drug and severity, as well

	as physical examination findings, vital sign measurements (supine systolic blood pressure [SBP] and diastolic blood pressure [DBP] and pulse), clinical laboratory results (hematology, including serum aminotransferases and serum lipids, coagulation, clinical chemistry, and urinalysis) and 12-lead ECGs. Descriptive statistics for observed values and change from Baseline will be calculated at each visit within each study period and by treatment group within cohort.
SAMPLE SIZE DETERMINATION	The first cohort of 15 adult subjects is a reasonable sample size to assess safety and tolerability before enrolling adolescents. Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively.. This study is not powered to detect a difference between the 2 active arms.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study periods for each subject will be as follows: 1. Screening: Up to 97 days. Before asking a subject to enter washout, investigators should confirm the subject meets study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined. 2. Double-blind study drug application: Twice weekly for 90 days. 3. Optional Open-label Extension: Twice weekly for 90 days. 4. Follow-up: 14 days after last study drug application. The maximum treatment duration for each subject is approximately 90 days for subjects who choose not to continue into the OLE, and 180 days for those who choose to continue. The maximum study duration for each subject is approximately 291 days.

2.2. Schedule of Events

Table 2-1: Schedule of Events for Double-blind Period

	Screening (--97 days to -1 day) Washout up to 90 Days [a]	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[b,c] ± 7 days (ET)
Visit	**1**	**2**		**3[d]**	**4[d]**		**5[d]**	**6[d]**
Written informed consent/assent	X							X
Assign screening number	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical history	X							
Physical examination	X	X[e]						X[e]
Vital signs (blood pressure and pulse)	X	X		X	X		X	X
Height, weight, and BMI	X							X[b]
IGA assessment[f]	X	X		X	X		X	X
VIIS[g] assessment	X	X		X	X		X	X
Roughness assessment[h]	X	X		X	X		X	X
Palm/sole assessment	X	X		X	X		X	X
Palm/sole fissuring assessment[i]	X	X		X	X		X	X
Ectropion score	X	X		X	X		X	X
Photographs[j]		X			X			X
Quality of life per Dermatology Life Quality Index (DLQI)		X		X	X		X	X
EQ-5D Quality of Life Questionnaire		X		X	X		X	X
12-lead ECG[k]	X	X			X			X

	Screening (--97 days to -1 day) Washout up to 90 Days [a]	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[b,c] ± 7 days (ET)
Visit	**1**	**2**		**3[d]**	**4[d]**		**5[d]**	**6[d]**
Clinical laboratory tests (hematology, chemistry, urinalysis)[l]	X	X			X			X
Serology (hepatitis B surface antigen, hepatitis C)	X							
Coagulation panel		X			X			X
Pregnancy test for female subjects (serum at Screening; urine subsequently)[m]	X	X			X		X	X
Randomization via IWRS		X						
PK blood sample collection[n]		X		X	X		X	X
Initial study drug application by clinic staff and measurement[o]		X						
Application instructions, advice on emollient and sunscreen use		X	X	X	X	X	X	X
Dispense study drug and diaries[p]		X		X[p]	X[p]		X[p]	(X)[p]
Concomitant medications	X	X	X	X	X	X	X	X
Tolerability assessment		X		X	X		X	X
Adverse events (and review diaries)		X	X	X	X	X	X	X
Collect all used/unused study drug[q]				X	X		X	X
Provide information about OLE option					X	X	X	X

Abbreviations: BMI = body mass index; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears, nose, throat; ICF = informed consent form; IGA = Investigator's Global Assessment; IWRS = interactive web response system; OLE = open-label extension; PK = pharmacokinetic; WOCBP = women of childbearing potential; VIIS = Visual Index for Ichthyosis Severity

a. Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and begin to washout prohibited topical and systemic treatments with designated washout periods, as applicable. Before asking a subject to enter washout,

investigators should confirm the subject meets study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined. During washout, subjects may continue their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard of care treatments in the electronic case report form (eCRF). If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower, but not bathe or swim, during the Screening Period.

b. Day 90 procedures should be conducted for subjects who terminate the study early. If a subject discontinues IP, but continues to attend clinic visits, Day 90 will occur as scheduled. Day 90 will be the first visit of the OLE for subjects who choose to continue. Subjects who decide to continue into the OLE will have the following additional procedures: 1) sign informed consent; 2) will be weighed; 3) will be instructed on study drug application; 4) will be given new diaries, and 5) will be provided with study drug.
c. A Follow-up telephone call will be made within 14 days after Day 90 to subjects who choose not to continue into the OLE to assess any ongoing adverse events.
d. Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 and unscheduled visits may be conducted remotely. Screening and Baseline Visits must be performed onsite only, and must be postponed or scheduled for when onsite visits can be safely conducted.
e. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
f. IGA: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe.
g. VIIS scale for each body area: chest/abdomen, back, legs, and arms, for a possible overall score = 16.
h. Roughness (0-4 scale);
i. Palm/sole fissuring assessment: present/absent/number/pain (0-3 scale).
j. Photography will be performed at sites with the capability for subjects who sign a photographic ICF. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check.
k. ECG to be conducted at Screening, Baseline, Day 30, and Day 90 for all subjects. Subjects in the PK substudy will also have postdose ECGs at each serial blood draw on Day 1 and Day 30.
l. Subjects must be fasting (i.e., at least 8 hours) for clinical laboratory tests, but not for PK blood draws.
m. Note: Subjects who are premenstrual at Screening but begin menses during the course of the study should follow the pregnancy testing schedule for WOCBP correlating to the visit menses began.
n. Samples for PK will be drawn from all subjects at Baseline and at each clinic visit. At selected sites among subjects who consent to participate in the PK substudy, samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1. On Day 30, IP will be applied in the clinic for PK substudy subjects, and PK samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose. Trough levels will be drawn when the subjects are in the clinic for other study visits (i.e., Day 14, Day 60, and Day 90). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.
o. Study staff will apply initial dose of study drug in the clinic after Baseline measurements, and the amount of study drug used will be measured (i.e., 36-g tube will be measured before and after application to determine amount used).
p. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug kits (tubes and box, but not leaflets) before dispensing; subjects must record days/times of study drug application in the diaries and any areas of skin not treated, e.g., due to local reactions. Dispense enough additional study drug until next visit (except at Day 90, unless subject consents to continue into OLE).
q. Confirm study drug compliance by weighing the study kits (tubes and boxes, but not leaflets) and reviewing diary.

Table 2-2: Schedule of Events for Open-label Extension

	Open-label Treatment Period[a]						Follow-up
	Telephone Visit (Day 97)	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7[a]**	**8[a]**		**9[a]**	**10**	**11[a]**
Informed consent[b]							
Physical examination[c]						X	X
Vital signs (blood pressure and pulse)		X	X	X	X	X	X
Record IGA[d]		X	X		X	X	X
VIIS[e] assessment		X	X		X	X	X
Roughness assessment[f]		X	X		X	X	X
Palm/sole assessment		X	X		X	X	X
Palm/sole fissuring assessment		X	X		X	X	X
Ectropion score		X	X		X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)[g]			X			X	
Pregnancy test for female subjects (urine)[h]			X		X	X	X
Coagulation panel			X			X	
12-lead ECG			X			X	
PK blood sample collection[i]			X			X	
Application instructions, advice on emollient and sunscreen use[j]	X	X	X	X			
Dispense study drug and diaries[k]		X	X		X		
Concomitant medications	X	X	X	X	X	X	X
Tolerability assessment		X	X		X	X	

	Open-label Treatment Period[a]						Follow-up
	Telephone Visit (Day 97)	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7[a]**	**8[a]**		**9[a]**	**10**	**11[a]**
Adverse events (and review diaries)	X	X	X	X	X	X	X
Collect all used/unused study drug[l]		X	X		X	X	

Abbreviations: ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears, nose, throat; ICF = informed consent form; IGA = Investigator's Global Assessment; PK = pharmacokinetic; OLE = open-label extension; VIIS = Visual Index for Ichthyosis Severity; WOCBP = women of childbearing potential

a. Although it is preferable to conduct all necessary study assessments in person (on -site visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 7-11 and unscheduled visits may be conducted remotely.
b. Subjects will sign the OLE ICF at the Double-blind Day 90 Visit. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing and PK from Day 90 will be carried over for the OLE and will not be repeated.
c. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
d. IGA: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe
e. VIIS scale for each body area: chest/abdomen, back, legs, and arms, for a possible overall score = 16.
f. Roughness (0-4 scale); fissuring assessment on palms/soles: present/absent/number/pain (0-3 scale).
g. Subjects must be fasting (at least 8 hours) for clinical chemistry testing, but not for PK only blood draws.
h. Subjects who are premenstrual at Screening but begin menses during the course of the study should follow the pregnancy testing schedule for WOCBP correlating to the visit menses began.
i. Samples for PK will be drawn from all subjects at Day 120 and Day 180. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.
j. Subjects must record days/times of study drug application in the diaries and any areas of skin not treated (e.g., due to local reactions).
k. All subjects in the OLE will receive trifarotene 200 µg/g. Study drug provided in 50-g tubes (maximum single application is 36 g). Weigh study medication kits (tubes and box, but not leaflets). Dispense enough additional study drug until the next visit (except at Day 180).
l. Confirm study drug compliance by weighing the study kits (tubes and boxes, but not leaflets) dispensed and returned and reviewing diary.

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

3.2. List of In-Text Figures

REASONS FOR AMENDMENT

Protocol Amendment 2 is a substantive amendment that addresses feedback from the Regulatory Agencies, Competent Authorities, Central Ethics Committees, and investigators. The following changes were made:

1. Changed all times defined as "weeks" to "days" throughout
2. Added new Section (Section 10.4) and Appendix B for procedural adjustments due to COVID-19.
3. Updated Phoevos Hughes' title.
4. Clarified that Cohort A may continue enrolling subjects until the DSMB considers it safe to open recruitment in Cohort B.
5. Clarified that washout periods apply to both prescription and over-the-counter medications.
6. Clarified that subjects receiving stable thyroid hormone medications with normal thyroid-stimulating hormone levels may be eligible for enrollment.
7. Clarified that subjects taking stable oral doses of Vitamin D analogs for at least 1 month at Screening may be eligible for enrollment.
8. Clarified and made consistent the definition of standard of care for visible skin (face and scalp) and of extremities (palms and soles).
9. Deleted "fixed dose" or "same amount" of IP throughout.
10. Aligned power calculation and parameter assumptions with the new primary endpoint.
11. Added optional photography evaluation of scoring by a central reader who is not a study investigator as a quality check.
12. Clarified that local tolerability comprises any stinging/burning, pruritus, or erythema and that each should be assessed on a 0-3 point scale.
13. As requested by the ethics committee in Germany, clarified that minor participants who reach majority during the study should be capable of providing informed consent for the PK substudy.
14. As requested by the ethics committee in Australia, clarified definition of women of childbearing potential and clarified that a hormonal vaginal ring or an IUD inserted at least 30 days before Baseline is an acceptable second form of contraception (i.e., IUD does not have to be hormonal).
15. Revised Exclusion Criterion #4 to define exclusionary levels of triglycerides and total cholesterol, and to allow subjects with normal levels of triglycerides and/or total cholesterol on stable doses of lipid-lowering agents for at least 6 months to be eligible for inclusion.
16. Revised Exclusion Criterion #10b with regard to exclusionary total bilirubin levels at Screening and defined acceptable levels for subjects with known Gilbert's Syndrome (>1.25 × upper limit of normal [ULN]).
17. Clarified Exclusion Criterion #13 to remove specific PR and QRS levels and heart rates.

18. Extended the Screening Period to allow for up to 90 days of washout, and clarified that all Screening procedures, with the exception of LI assessment, should be performed before a subject begins the Washout Period. The subject will return after completing the washout period for LI assessment and to confirm eligibility.
19. Revised Figure 7-1 and Figure 7-2 to correct typos and to change weeks to days.
20. Revised Table 2-1 and Table 2-2 to correct timing and omissions.
21. Clarified the intervals between IP applications and added a table to illustrate a twice-weekly schedule.
22. Removed location for Catalent Pharma Solutions.
23. Clarified that subjects who participate in the PK substudy should have their Day-30 Visit scheduled on a treatment day, and that investigators should contact the medical monitor if that is not possible.
24. Added a coagulation panel to the study procedures.
25. Added the composition and qualifications of the DSMB.

SUMMARY OF AMENDED SECTIONS – SUBSTANTIVE AMENDMENT

Section	Previous Text	Revision	Rationale
Title throughout document	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 12-week Safety, Efficacy, and Systemic Exposure Study followed by a 12-week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, **90-Day**, Safety, Efficacy, and Systemic Exposure Study followed by a **90-Day** Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale	To be more precise about time intervals
Document	"Weeks"	Changed all to days	To be more precise about time intervals
Synopsis and Section 7	Adults (Cohort A) and adults and adolescents (Cohort B) will be randomized in a double-blind fashion to 1 of 2 doses of trifarotene cream HE1 or vehicle and treated twice weekly for 12 weeks. If no safety issues are identified, both adults and adolescents (ages 12 to 17 years, inclusive) will be allowed to enroll together with adults in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks in the same manner as subjects in Cohort A.	Adults and adolescents will be randomized in a double-blind fashion to 1 of 2 doses of trifarotene cream HE1 or vehicle and treated twice weekly for **90 days**. If no safety issues are identified, adolescents (ages 12 to 17 years, inclusive) will be allowed to enroll together with adults in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly **for 90 days** in the same manner as subjects in Cohort A. Added: Cohort A will continue enrolling only adult subjects until the DSMB considers it safe to open recruitment in Cohort B	To clarify To clarify and ensure protocol memo (nonsubstantial change) is captured in the protocol
Synopsis and Section 9.8	Upon signing informed consent and entering the Screening Period, subjects may begin washout, during which they will stop using physical and medical treatments for LI, including balneotherapy, and the following prohibited medications, as applicable.	Upon signing informed consent and entering the Screening Period, subjects may begin **a Washout Period of up to 90 days**. Participants will stop using physical and medical treatments for LI, including balneotherapy, **as well as** the following prohibited medications, as applicable**.** Added: the following list applies to both prescription and over-the-counter medications:	To clarify

Section	Previous Text	Revision	Rationale
Synopsis and Section 9.8	Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines. (except Vitamin D analogs taken at stable dose since at least 1 month.	Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones **unless the dose is stable and thyroid-stimulating hormone (TSH) is normal**, cytotoxics, bisphosphonates, **selective estrogen receptor modulators (SERM), teriparatide,** calcitonins, tetracyclines, quinolones, thiazides, **long-term use of** salicylates, heparin, theophylline, barbiturates, colchicines. Vitamin D analogs taken at stable dose **for at least 30 days are allowed.**	Added prohibited medications and clarified which medication interfering with bone activity is acceptable.
	Enzyme inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	**CYP** enzyme inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	To clarify
	CYP2C9 and 2C8 inhibitors (not all inclusive, gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	CYP2C9 and 2C8 inhibitors **(including, but not limited to the following**: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	
	Monoclonal antibody treatment (e.g., anti IL17	Monoclonal **antibodies**	

Section	Previous Text	Revision	Rationale
Synopsis, Table 2-1 footnote a, and Sections 7.1, 9.8, and 10.2.1.1 and 10.2.1.1.1	During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hand/feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower, but not bathe or swim, during the Screening Period. After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements. Subjects may shower, but not bathe or swim. After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.	Added: Before asking a subject to enter washout of their prescription and over-the-counter prohibited treatments, investigators should confirm the subject meets all study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and to complete study eligibility requirements During washout, subjects may continue **their standard of care** of visible skin (face and scalp) for cosmetic reasons and of extremities (**palms/soles**) to avoid functional consequences on walking or moving their fingers. **In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard-of-care treatments in the electronic case report form (eCRF). If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit.** Subjects may shower, but not bathe or swim.	To ensure subjects do not have to repeat Screening assessments after washout. To better define standard of care and prevent confusion.

Section	Previous Text	Revision	Rationale
Synopsis and Section 7.1	Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied.	Study staff will **choose 1 tube from the kit dispensed to the subject at that visit, and apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements; they will weigh the study tube before and after application to determine the amount used.** Added: The kit dispensed at baseline must be weighed before the first tube is chosen for application by the study staff. Weight of the kits dispensed and returned by the subject during the study includes both tubes and cartons, but not leaflets, which need to be removed before weighing. The subject must be reminded to return the kits with tubes and cartons, whether used or not, when returning to the next visit.	To clarify how amount of IP applied is determined To ensure kits are weighed appropriately before dispensing to the subject and upon return
Synopsis	Thereafter, each subject will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas.	Thereafter, each subject will apply study drug on up to 90% of BSA twice weekly **3 to 4 days apart,** sparing the scalp, inguinal, and axillary areas. Added: **Subjects with heavy facial hair should not apply IP to hair-bearing areas**. Added: The study protocol limits application of IP to 36 g maximum; no additional tubes can be given, whether during the randomization period or the OLE period. If the study staff and subject note that there is insufficient volume for full body application, the subject should apply trifarotene cream sparingly twice weekly to the most affected areas, and always to the same skin areas. Study cream should be very sparingly applied. Trifarotene cream 100 or 200 µg/g, is a highly potent topical retinoid and it is not necessary to apply much for efficacy; application of more will increase the risk of irritation and systemic penetration.	Removed fixed amount/same amount because of the natural variations in the extent and severity of LI. To not apply IP to hair-bearing areas for the first 90 days. To address questions about the amount of cream to apply when a single tube does not seem to be enough

Section	Previous Text	Revision	Rationale
Synopsis, Sections 7.1, 9.4, and 13.1.6.1	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for stinging/burning, pruritus, erythema) for each body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed: - If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas. - If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas.	During all clinic visits, the investigator will assess local tolerability (**stinging/burning, pruritus, or erythema on 0-3 scales** [none, mild, moderate, severe]) for each body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed: - If a score of 2 (moderate) is recorded **for any of the** local tolerability assessment scale**s** (stinging/burning, pruritus **or** erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas. - If a score of 3 (severe) is recorded **for any of the** local tolerability assessment scale**s** (stinging/burning, pruritus **or** erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas.	To clarify that any of the 3 local tolerability conditions may warrant modification of dosing frequency

Synopsis		Added: The coronavirus disease 2019 (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted in order to control the spread of the disease. It is recommended that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19. Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19 - related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 (Double – blind Period; Table 2-1), Visits 7-11 (OLE Period; Table 2-2) and unscheduled visits may be conducted remotely. Screening and Baseline Visits must be performed on site only. These visits must be postponed or scheduled for when onsite visits can be safely conducted. The following assessments may occur remotely: • Safety Assessments o Concomitant medications and concomitant therapies. o Adverse Events and related information reported by the patient in the diary o General health status of the patient • Tolerability Assessments • Pregnancy Tests: Urine pregnancy tests along with the instructions on proper use will be sent to the subject's home for women of childbearing potential (WOCBP). Study staff will instruct patient to perform the urine pregnancy at the applicable remote visit. • Study Medication Supply: As necessary and according to applicable local regulations, study medication will be sent to subjects.	

Section	Previous Text	Revision	Rationale
		• DLQI and EQ-5D Questionnaires: Quality of Life questionnaires should be completed on the day of the remote visit and prior to applying treatment (if the remote visit falls on a treatment day). Questionnaires may be sent to subjects electronically or via postal service, and completed questionnaires may be returned to the site in the same manner. If subjects are unable to send completed questionnaires to the site, investigators should ask and record the subject's responses during the remote visit. • Patient Diary: Patient diaries may be sent to subjects electronically or via postal service. Completed diaries may be returned to the site in the same manner.	

Synopsis and Section 8.2.1	6. Subject who is participating in the optional PK substudy has signed a PK ICF. 7. Subject is not of childbearing potential, i.e., a female who has not yet begun menstruating or who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason), hysterectomy or bilateral oophorectomy, combined oral contraceptives (estrogens and progesterone), or implanted or injectable hormonal contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline […] • Note: Subjects who are premenstrual at Screening but begin menses during the study should follow the pregnancy testing schedule for WOCBP and must abstain from sexual intercourse while in the study and for at least 1 month after the last study drug application.	6. Subject who is participating in the optional PK substudy has signed a PK ICF. **Minors, in the event of their reaching majority during the study, should be capable of giving consent to take part in the PK study.** 7. Subject is not of childbearing potential, who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason), or has documented hysterectomy, **bilateral salpingectomy**, or bilateral oophorectomy. **For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.** OR Subject is a woman of childbearing potential (WOCBP), **i.e. a female ≥12 years of age (regardless of whether they have experienced/reported menarche)**, or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception: • bilateral tubal ligation • combined oral contraceptives (estrogens and progesterone), **vaginal ring**, or implanted or injectable **hormonal** contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation • intrauterine device (IUD) inserted at least **30 days** before Baseline […] • Note: **Female subjects** who are premenstrual at screening should **nonetheless** follow the	The change in Inclusion Criterion #6 was requested by the German Central Ethics Committee. Clarified definition of WOCBP. Clarified that a hormonal vaginal ring or an IUD inserted at least 30 days before Baseline is an acceptable form of contraception (i.e., IUD does not have to be hormonal). This change was requested from the RCH Human Research Ethics Committee (HREC) in Australia

Section	Previous Text	Revision	Rationale
		pregnancy testing schedule for WOCBP **even if they** abstain from sexual intercourse while in the study and for at least 1 month after the last study drug application.	
Synopsis and Section 8.2.2	4. Subjects with a known lipid disorder (hypertriglyceridemia >200 mg/dL, hypercholesterolemia >250 mg/dL. a. Subjects whose triglyceride and/or total cholesterol are within normal limits with stable dose of lipid-lowering agents for at least 6 months can be included.	4. Subject with **fasting triglycerides** >200 mg/dL **or >2.25 mmol/L and/or total cholesterol** >250 mg/dL **or >6.5 mmol/L**. Subjects whose triglycerides and/or total cholesterol are within normal limits with a stable dose of lipid-lowering agents for at least 6 months **may be** included.	To clarify laboratory parameters per laboratory units
	7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis).	7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis). **Subjects with hypothyroidism who are on a stable dose of thyroid hormone replacement therapy and whose TSH is normal may be included.**	To permit subjects with hypothyroidism on stable treatment with normal TSH to be enrolled.
	10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory b. Total bilirubin >1.1 mg/dL at screening, or, in case of Gilbert's syndrome total bilirubin >3 mg/dL	10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal **(ULN)** defined by the laboratory b. Total bilirubin **>1.25** × ULN at Screening. **Subjects with known** Gilbert's syndrome **may be included with total bilirubin >1.25 × ULN**	To clarify laboratory parameters for exclusion
	13. Subject has a history of long QT syndrome or has clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, or QTcF interval >450 ms, PR interval is not between 120 and 220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed	13. Subject has a history of long QT syndrome or has clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, or QTcF interval >450 ms	To clarify because there is a high number of left anterior hemiblocks without clinical significance among screened subjects. In these cases, the QRS Interval can be above normal

Section	Previous Text	Revision	Rationale
Synopsis	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Extension dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 200 µg/g applied topically twice weekly on up to 90% BSA	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: Up to 36 g per dose of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Extension dose, route, frequency: Up to 36 g per dose of 200 µg/g applied topically twice weekly on up to 90% BSA	Fixed dose is no longer applicable.
Synopsis and Section 10		Added: coagulation panel to all visits at which blood and urine are collected for laboratory tests	To correct an omission
Synopsis and Section 10.1.1	1. Screening: Up to 35 days (after signing informed consent, if necessary, washout may be up to 3 months, and subjects should return to the site after washout to complete the study eligibility requirements). 2. Double-blind study drug application: Twice weekly for up to 12 weeks. 3. Optional Open-label Extension: Twice weekly for up to 12 weeks. 4. Follow-up: 14 days after last study drug application. The maximum study duration for each subject is approximately 229 days (33 weeks). The maximum treatment duration for each subject is 24 weeks	1. Screening: Up to **97 days. Before asking a subject to enter washout, investigators should confirm the subject meets study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days**. **After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined** 2. Double-blind study drug application: Twice weekly for **90 days**. 3. Optional Open-label Extension: Twice weekly for **90 days**. 4. Follow-up: 14 days after last study drug application. The maximum treatment duration for each subject is approximately **90 days for subjects who choose not to continue into the OLE, and 180 days for those who choose to continue.** The maximum study duration for each subject is approximately **291 days**	To reflect the change from weeks to days, and to allow sufficient time for the washout period (up to 3 months) and adjust the study periods accordingly

Section	Previous Text	Revision	Rationale
Synopsis and Section 13.1.4.1	Secondary: The secondary endpoints are as follow: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Week 12: ▪ 5-point VIIS scale for scaling from Baseline through Week 12 ▪ Individual score for roughness (Scale: 0–4) overall • The difference in proportion of subjects with presence of fissures on palm/soles (presence/absence, number of fissures, and pain associated with fissures [on a 0-3 scale]) at Week 12 between the active trifarotene cream HE1 and vehicle groups	Secondary: The secondary endpoints are as follow: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through **Day 90**: ▪ 5-point VIIS scale for scaling ▪ Individual score for roughness (Scale: 0–4) • The difference in proportion of subjects with presence of fissures on palm/soles (presence/absence, number of fissures, and pain associated with fissures [on a 0-3 scale]) at **Day 90** between the active trifarotene cream HE1 and vehicle groups	To reflect the change from weeks to days
Synopsis and Section 13.1.4.1	Safety endpoints: – Local tolerability (Scale: 0-3 [none, mild, moderate, severe], determined by the investigator) for each body area (chest/abdomen, back, legs, arms, and face/neck).	Safety endpoints: – Local tolerability (**stinging/burning, pruritus, or erythema on 0-3 scales** [none, mild, moderate, severe]) for each body area (chest/abdomen, back, legs, arms, and face/neck).	
Table 2-1		Height, weight, and BMI were added to Screening from Baseline Coagulation panel was added at Baseline, Day 30, and Day 90 Dispense study drug and diaries was added at Day 90 Added footnote: d Although it is preferable to conduct all necessary study assessments in person (on -site visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 and unscheduled visits may be conducted remotely. Screening and baseline visits must be performed onsite only, and must be postponed or scheduled for when onsite visits can be safely conducted.	To clarify when procedures are to be done To provide procedural accommodations due to COVID-19

Section	Previous Text	Revision	Rationale
Table 2-2		Vital signs (blood pressure and pulse) was added at Day 150 Ectropion score was added at Day 104 and Day 150 and removed at Day 134. Coagulation panel was added at Day 120 and Day 180 Added footnote: a. Although it is preferable to conduct all necessary study assessments in person (on -site visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 7-11 and unscheduled visits may be conducted remotely.	To clarify when procedures are to be done To provide procedural accommodations due to COVID 19
Section 5.2	Throughout the 30 clinical studies that comprise the clinical development program for CD5789 topical products, 1976 subjects were exposed to CD5789	Throughout the **31 completed** clinical studies that comprise the clinical development program for CD5789 topical products, **4878** subjects were exposed to CD5789	Updated for latest data
Section 6.2	• To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.	• To assess safety for up to **180 days** of dosing **with trifarotene cream HE1 200 µg/g**.	Subjects will only receive open-label trifarotene cream HE1 200 µg/g for 90 days.
Synopsis, Section 7.1, and Section 10.2.4 (OLE)	The first cohort of subjects (Cohort A) will randomize approximately 15 adults (≥18 years old) in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle…. All subjects (Cohort A and Cohort B) who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for up to 12 weeks. During the OLE, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and Week 24 from all subjects who continue into the OLE (Table 2-2).	The first cohort of subjects (Cohort A) will randomize adults (≥18 years old) in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle…. All subjects who complete the Double-blind Treatment Period will be eligible to enroll in the OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly. During the OLE, subjects will return to the site at **Days 104**, **120, 150, 180, and 194**. Additional PK samples will be drawn at **Days 120** and **180** from all subjects who continue into the OLE (Table 2-2).	To allow more than 15 subjects to enroll in Cohort A (because it will continue enrolling only adult subjects until the DSMB considers it safe to open recruitment in Cohort B. To be more precise with timing

Section	Previous Text	Revision	Rationale
Section 7.2	To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of 15 adults randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly. If no safety issues are identified, 105 adults and adolescents (ages 12–17 years, inclusive) will be allowed to enroll in Cohort B and randomized to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly in the same manner as subjects in Cohort A.	To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of adults randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly. If no safety issues are identified, adults and adolescents (ages 12–17 years, inclusive) will be allowed to enroll in Cohort B and randomized to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle **and** treated twice weekly in the same manner as subjects in Cohort A**.**	To allow flexibility in enrollment numbersTo align power calculation and parameter assumptions with the new primary endpoint.
Section 8.4	8.4 Discontinuation of Study Intervention Discontinuation from study treatment does not mean withdrawal from the study, and the remaining study procedures should be completed as indicated in the study protocol (see Section 10.2.4.5)	8.4. Subject Discontinuation of Study Intervention **and Stopping Rules** **Subjects who discontinue the study treatment will be asked to return to the site to undergo ET procedures (Section 10.2.4.6)**	To clarify and to link to correct section.
Section 9.1		Added: Sodium benzoate, butylhydroxytoluene, and propylene glycol are excipients known to have a recognized action or effect to be declared on the labeling, according to the CHMP Annex to the excipients in labeling and package leaflet of medicinal products for human use (EMA/CHMP/302620/2017). These 3 excipients are being used in the trifarotene formulation at standard concentrations and are all necessary to ensure adequate protection of the formulation along and the shelf life.	To fulfill request by French CA

Section	Previous Text	Revision	Rationale
Section 9.2	For the Double-blind Treatment Period, a fixed dose (determined at Visit 2) of trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject.	For the Double-blind Treatment Period, trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject.	To remove fixed dose and allow dosing to be based on BSA
	Subjects will continue treatment for up to 12 weeks	Subjects will apply treatment for 90 days.	Clarification and precision of timing
	For the OLE, all subjects will receive trifarotene cream HE1 200 µg/g and apply it the same fixed dose same manner as in the Double-blind Period for an additional 12 weeks.	For the OLE, all subjects will receive **open-label** trifarotene cream HE1 200 µg/g and apply it in the same manner as in the Double-blind Period for an additional **90 days**.	Clarification and precision of timing
Section 9.3	After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply approximately the same amount of IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week, at least 3 days apart, on which to apply their IP (e.g., Tuesday and Friday), and maintain that regimen throughout the study. Subjects should not apply the IP on visit days until after the visit, unless they participate in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the predose PK blood draw.	After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week, **3 to 4 days apart**, on which to apply their IP, and maintain that regimen **each week** throughout the study (Table 9-1). **Subjects whose treatment day falls on a scheduled study visit** day should not apply the IP until after the visit. **Subjects who** participate in the PK substudy **should have their Day 30 Visit scheduled on a treatment day,** in which case the IP will be applied in the clinic on Day 30 after the predose PK blood draw. Added: **If the Day 30 Visit cannot be scheduled on a treatment day, the investigators should contact the medical monitor.**	To specify that treatment applications should be 3 to 4 days apart, and that PK substudy subjects must visit the clinic on Day 30.
	If a subject misses an IP application, they should apply the IP as soon as they remember and record the date/time in the subject diary.	Added: **The next application should be 3 to 4 days apart and subjects should continue according to their new regimen.**	To specify treatment day interval
	Subjects who continue into the Open-label Extension will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the Double-blind Period for an additional 12 weeks	Subjects who continue into the OLE will receive trifarotene cream HE1 200 µg/g and apply in the same manner as in the Double-blind Period for **90 days**	To remove fixed dose and allow dosing to be based on BSA
		Added: Table 9-1: Sample Twice-weekly Dosing Schedule	To provide a visual example of dosing schedule options
Section 9.4		Deleted Section 9.4.1 Stopping Rules	Section was redundant with Section 8.4

Section	Previous Text	Revision	Rationale
Section 9.5	Study personnel will assess treatment compliance with IP regimens by weighing IP tubes before dispensing and upon return and by questioning the subject, at every postrandomization visit. A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, supplemented by tube weight. A subject who is not compliant (used 80–120% of IP tubes) will be counseled at each visit on the importance of using the IP as instructed.	Study personnel will assess treatment compliance with IP regimens **by weighing kits (tubes and boxes, but not leaflets)** before dispensing and upon return and by questioning the subject at every post randomization visit. **At baseline, the kit should be weighed before choosing the first tube for application by the study staff.** A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, **supplemented by amount of cream used derived from weighing the IP kits**. A subject who is not compliant (for example, used <80 or >120% of IP tubes **[which is more than what can be dispensed per tube at each application]),** the subject will be counseled at each visit on the importance of using the IP as instructed.	
Section 10.2.2.7	Subjects will have up to 7 days to decide to enter the OLE; if the subject chooses to continue into OLE, the following additional procedures will be done: ….Remind subjects that at least 24 hours must have elapsed since IP application before the PK draws at the Week 16 and Week 24 Visits, and not to apply IP on visit days until after the visits.	If the subject chooses to continue into OLE, the following additional procedures will be done Revised: Remind subjects that at least 24 hours must have elapsed since IP application before the PK draws at the **Day 120** and **Day 180** Visits, and not to apply IP on visit days until after the visits.	Subjects must decide by Day 90 if they want to continue into the OLE.
Section 10.2.4.1	Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and to remind subjects not to apply IP on visit days until after the visit.	Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and to remind subjects not to apply IP on visit **Days 120 and 180** until after the visit.	Day 120 and Day 180 include PK draws, so IP should be applied after the visit is complete.

Section	Previous Text	Revision	Rationale
Section 10.2.4.2	12. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit at the Week 16 and Week 24 Visits, and not to apply IP on visit days until after the visit.	12. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit **(Day 120) and if the Day 120** visit **coincides with a treatment day, wait** until after the visit **is complete** to apply IP.	To specify timing of IP application
Section 10.2.4.5		Added: 13. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit (Day 180) and if the Day 180 visit coincides with a treatment day, wait until after the visit is complete to apply IP.	To specify timing of IP application
Section 10.2.4.7	10.2.4.7 Follow-up Evaluation – Open-Label Extension Week 26/Visit 11)	10.2.4.7 Follow-up Evaluation – Open-Label Extension (**Day 194 or 14 days after End of Open label Treatment** /Visit 11)	To be more specific

Section	Previous Text	Revision	Rationale
Section 10.4 and Synopsis		New section: 10.4. Procedural Adjustments Due to COVID-19 The coronavirus (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted to control the spread of the disease. It is recommended that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19. Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 (Double-blind Period; Table 2-1), Visits 7-11 (OLE Period; Table 2-2) and unscheduled visits may be conducted remotely. Screening and baseline visits must be performed onsite only, and must be postponed or scheduled for when onsite visits can be safely conducted. Appendix B details the procedures when it is inadvisable or not possible to conduct an onsite study visit.	To provide procedures/schedule for COVID-19 issues.
Section 11.2.1		Added: The Tolerability Assessments Form at each visit collects a numeric severity score by body area for erythema, stinging/burning, and pruritus. In addition, if skin irritation is more than the expected erythema, stinging/burning, and pruritus with the application of this topical retinoid (i.e., clinically relevant), please enter the application site reactions in the Adverse Event description section. If a diagnosis is known, record the diagnosis. If a diagnosis is known and there are other signs/symptoms that are not generally part of the main diagnosis, record the diagnosis and each sign/symptom on a separate line. If a diagnosis is not known, record each sign/symptom on a separate line. Examples are allergic contact dermatitis, sunburn, skin erosion, and swelling.	To specify how tolerability assessments are collected.

Section	Previous Text	Revision	Rationale
Section 11.2.2.3	Dose reduced An indication that a medication schedule was modified by subtraction, either by changing or reducing the frequency, strength, or amount.	Dose reduced An indication that a medication schedule was modified by **reducing the frequency of application**	Dose cannot be reduced by changing the strength or amount.
Section 11.3.2	These findings must be reported on the Exposure in Utero form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.	Deleted: The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an SAE and AE form (entering the event temporarily as nonserious on both forms) provided by the sponsor or its designee. These findings must be reported on the **Pregnancy Data Collection Form** and forwarded to **Premier Research Pharmacovigilance**. The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly. **In such case an additional form (Serious Adverse Event Report Form) must be filled out by the Investigator and provided to Premier Research Pharmacovigilance within 24h of knowledge of the pregnancy's serious outcome.**	Repetitive; AE forms not collected by pharmacovigilance
Section 12		Added names and qualifications of the DSMB The DSMB committee members are as follow: • Univ. Prof. Dr. med. Steffen Emmert, Director at Clinic and Polyclinic for Dermatology & Venereology • Jeffrey Louis Sugarman, M.D., Ph.D. • Moise L. Levy, MD, Pediatric Dermatologist • Gabriele Accetta, Ph.D. Biostatistician	In accordance with French Ethics Committee
Section 13.1.1		Added: Deviations related to COVID-19 will also be evaluated in determining Per-protocol Population eligibility.	To provide COVID-19 information
Section 13.1.4		Added: Efficacy endpoints will be based on investigator assessment.	To specify that investigator assessment is primary for efficacy

Section	Previous Text	Revision	Rationale
Section 13.1.4.5		Added: Thorough assessment on the extent of missing data and procedural adjustments due to COVID-19 as it pertains to the primary and secondary efficacy endpoints will be conducted ahead of database lock and additional sensitivity analyses may be performed. Full details will be documented in the SAP.	To provide contingency methods for COVID-19 issues
Section 14.3		Added: Subjects may only be rescreened once 30 days or more after the original Screening Visit.	Subjects should be rescreened if the reason for SF is reasonably believed to have been resolved.
Section 15	The final CSR will be written within 1 year of completion of the clinical part of the study. For pediatric studies, the final CSR will be written within 6 months.	The final CSR will be written within **6 months** of completion of the study.	This study involves pediatric subjects.
Appendix B		Added new Appendix B with Procedural Adjustments for COVID-19	To provide guidance for remote visits during COVID-19

AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ATC	anatomical therapeutic chemical
AUC	area-under-the-curve
BMI	body mass index
BSA	body surface area
CFR	code of federal regulations
CI	confidence interval
C_{max}	maximum concentration
COVID-19	Coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressure
DLQI	dermatology life quality index
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ESS	ectropion severity score
FDA	Food and Drug Administration
GCP	good clinical practice
GEE	generalized estimating equations
HR	heart rate
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IND	investigational new drug
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IWRS	interactive web response system
LI	lamellar ichthyosis
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
MMRM	mixed model of repeated measures
NCA	noncompartmental analysis

ABBREVIATION	EXPLANATION
OC	observed case
OLE	open-label extension
OTC	over-the-counter
PG	propylene glycol
PK	Pharmacokinetic(s)
PoC	proof-of-concept
PP	per-protocol
QTc	QT interval corrected for heart rate
RARγ	retinoid acid receptor γ
RBC	red blood count
RR	respiratory rate
RXR	retinoid X receptor
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
TEAE	treatment-emergent adverse event
T_{max}	time of C_{max}
TSH	thyroid-stimulating hormone
UAE	unexpected adverse event
UADR	unexpected adverse drug reaction
ULN	upper limit of normal
US	United States
UV	ultraviolet
VIIS	Visual Index for Ichthyosis Severity
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

5. INTRODUCTION

5.1. Background and Rationale

The ichthyoses comprise a large group of skin scaling disorders with diverse etiology. The stereotypic pathophysiology is epidermal hyperplasia and the formation of excess stratum corneum accompanied by abnormal (delayed and/or disordered) desquamation, with visible accumulation of squames (scales) on the skin's surface – the clinical hallmark of all the ichthyoses.

Lamellar ichthyosis (LI) is recognized as a severe form of ichthyosis that persists throughout life. During the first postnatal weeks, the hyperkeratotic membrane patients are typically born with is gradually shed, and is replaced by scaling and lichenification that involves the entire body including the intertriginous areas, palms, soles, and scalp. While usually not life threatening, LI can result in disability, partial deafness, poor adaptation to environmental conditions (due to hypohydrosis), severe discomfort (pruritus, fissuring of the skin) and significant psychosocial impact.

Lamellar ichthyosis, a member of the nonsyndromic autosomal recessive congenital ichthyosis group of ichthyoses, has an incidence of 1 per 100,000-300,000 live births.[1] Lamellar ichthyosis is undoubtedly a rare disease.

Therapeutic approaches for LI are mainly based on the use of topical emollients, keratolytic agents (urea, lactic acid, salicylic acid), topical retinoids and, in severe cases, oral retinoids.[2,3]

Oral retinoid usage in LI is mainly based on case reports and case series.[4,5,6,7,8] The mechanism of retinoid action involves modulation of keratinocyte differentiation, keratinocyte hyperproliferation and tissue infiltration by inflammatory cells. Systemic retinoids (such as acitretin, etretinate, or isotretinoin) have been found to be efficacious in the treatment of severe ichthyoses, especially in LI.[6]

Vahlquist, et al (2008)[3] report that by combining 2 or more keratolytic agents and moisturizers in the same lipophilic cream base, it is often possible to achieve additive or even synergistic effects in LI without the need to use irritating concentrations of either agent alone. In a double-blind trial of 4 different cream mixtures in 20 patients with LI, a mixture of 5% lactic acid and 20% propylene glycol (PG) in a semi-occlusive cream for 4 weeks twice daily was significantly more effective than 20% PG or 5% urea alone in the same vehicle.[9] Although the treatments were well tolerated, an efficient removal of hyperkeratosis without correcting the underlying biochemical defect in LI is likely to deteriorate the patient's intrinsic barrier problem, because an excessive production of corneocytes probably represents a homeostatic response to an ineffective barrier. Indeed, transepidermal water loss increased after successful treatment of LI with either topical keratolytics[9] or oral retinoid.[10] Although this may not be noticeable by the patient, even minor deteriorations in the barrier function can enhance transcutaneous penetration of active cream ingredients or other topically applied chemicals, which is a matter of special concern in children. Accordingly, α-hydroxy acids and salicylic acid should not be used at all in babies and only with great caution when treating large, eroded skin areas in adult patients.[11,12]

Many patients with LI use pumice, foot files, or gentle rubbing of the skin after a hot bath or a shower to remove scales and hyperkeratosis. Overnight occlusion of problematic skin areas with plastic sheets after applying a thick layer of emollient or keratolytic agents is another way of potentiating therapy, especially on the scalp, which is notoriously difficult to treat. Although

usually effective, all these remedies may further damage the skin barrier and lead to exaggerated epidermal proliferation, erythema, painful erosions and increased transcutaneous penetration.[3]

Based on this information, LI has significant unmet medical need for safer and more effective therapies.

5.1.1 CD5789 (Trifarotene)

CD5789 is a new chemical entity discovered by Galderma R&D SNC and formulated for topical application. It is a novel retinoid acid receptor γ (RARγ) agonist, characterized by its high specificity to this receptor. CD5789 is selective for RARγ over RARα and RARβ (approximately 50- and 8-fold, respectively), with no retinoid X receptor (RXR) activity. CD5789 is currently under clinical development for the topical treatment of various dermatoses, including acne vulgaris and LI.

The pharmacological retinoid-like properties of CD5789 were confirmed in in vitro and in vivo models, showing its interest for its development in the treatment of LI. Therefore, it may have an effect on the differentiation and hyperproliferation of keratinocytes, and consequently improve hyperkeratotic skin of patients with lamellar ichthyosis.

Within the overall acne development program at Galderma, CD5789 has been tested in different pharmaceutical forms for topical administration. As of 15-Jan-2018, 6 different formulations have been evaluated: a solution, a gel and 4 creams (CD5789 cream A, CD5789 cream B, CD5789 cream HE1 concept and its optimized version, cream HE1), with different concentrations (up to 400 µg/g). Therefore, several formulations at different CD5789 concentrations have been tested in nonclinical and clinical development programs.

Galderma decided to develop a new cream formulation that might better address the issue of skin dryness in patients with LI. This formulation was named “Cream HE1 concept.” It has been preliminarily investigated in an exploratory trial in psoriasis at concentrations up to 400 µg/g (RD.03.SRE.40204E). In a proof-of-concept study (RD.03.SRE.40181E), positive results were also obtained in patients with LI with CD5789 cream (up to 100 µg/g) that was effective in decreasing scaling and roughness. Based on these results, a new CD5789 formulation (cream HE1) was developed for further clinical investigations in LI. The formulation cream HE1 was developed with the objective to obtain a formulation with appropriate stability of the active ingredient and in which CD5789 would be homogeneously dissolved in the oily phase at a higher concentration compared to the cream formulation used in the acne program. Cream HE1 contains 100, 200, or 400 µg/g (0.01% [w/w], 0.02% [w/w], 0.04% [w/w], respectively) of CD5789.

Galderma has granted Mayne Pharma LLC an exclusive license to develop and commercialize CD5789 (trifarotene) for LI and other orphan diseases; therefore, the LI indication is no longer pursued by Galderma.

5.2. Clinical Experience

The cream HE1 differs from the CD5789 cream used to treat acne vulgaris in that it contains fewer excipients with drying effects and therefore may be better suited for patients with LI.

Throughout the 31 completed clinical studies that comprise the clinical development program for CD5789 topical products, 4878 subjects were exposed to CD5789. No systemic safety concerns related to CD5789 gel or creams, or cream HE1 at doses up to 400 µg/g were reported. The subjects

were exposed to a maximal total CD5789 dose of 36 g/day (Investigator's Brochure for CD5789 Cutaneous Formulation).

One study was conducted with CD5789 50 µg/g, 100 µg/g, and placebo in subjects with ichthyosis (Study RD.03.SRE.40181E). Among 31 subjects treated in this study, 17 were treated with CD5789 100 µg/g, and 14 were treated with 50 µg/g (all subjects received placebo [vehicle] on the contralateral zone). Mean (SD) baseline IGA score was 5.7 ± 1.6 among the 31 subjects. Improvement in the investigator's global assessment (IGA) of scaling and roughness was observed by Day 8 with both doses. The primary efficacy criterion was the change in IGA from the Baseline Visit (Day 1) to the Final Visit (Day 43). At Endpoint (intent-to-treat population, last observation carried forward [LOCF]), the CD5789 100 µg/g group had a statistically significant decrease from Baseline in IGA compared with Vehicle (-1.4±2.2; p=0.018) (Investigator's Brochure for CD5789 Cutaneous Formulation).

The CD5789 PK profile was also investigated using cream HE1 (Study GD.03.SRE.103813) in 36 healthy volunteers of Japanese and non-Japanese origin. Subjects were treated daily on up to 90% of body surface area (BSA) for 29 days with up to 36 g of cream formulation. Both CD5789 100 µg/g and 200 µg/g cream HE1 were investigated. Plasma PK assessment demonstrated that repeated topical applications of CD5789 cream HE1 resulted in low and similar CD5789 systemic levels in all treatment groups. In addition, no systemic safety concerns were raised from this healthy volunteer study in which cream HE1 200 µg/g was applied daily under maximal-use conditions on almost the full body. In this study, however, the level of irritation resulted in the need to decrease the frequency of application to twice weekly (Investigator's Brochure for CD5789 Cutaneous Formulation). However, it is possible that absorption in subjects with LI may be greater than in healthy volunteers, due to the skin being compromised.

Based on these data, both the 100 µg/g and 200 µg/g doses showed an acceptable safety profile and will be used in this phase 2 LI study, to determine which of the 2 doses is most effective. The open-label extension (OLE) will evaluate the long-term safety of the higher dose in this patient population.

5.3. Summary of Potential Risks and Benefits

Although the primary objective of this study is safety in the patient population with LI, the potential benefits of study participation are that subjects with LI may experience a reduction in their LI symptoms as a result of treatment with trifarotene (CD5789) cream HE1. No other benefits of participation are anticipated.

The potential risks of study participation for all subjects include those associated with exposure to trifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture. The study population will comprise adults and adolescents aged 12 to 17 years.

Animal studies with CD5789 have shown reproductive toxicity in the embryo-fetal studies. Despite low systemic levels with the CD5789 concentration of 50 µg/g used in patients with acne, CD5789 must not be administered during pregnancy.

When CD5789 is used in the other formulations and/or for other indications and/or with higher concentrations or higher application surface areas, the potential risk of teratogenicity needs to be considered as the safety margin may be lower. Depending on the study population and conditions mentioned above, or other specific requirements, the appropriate contraception method is described in this protocol.

It is unknown whether CD5789 or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Lactating women are not eligible for the clinical study.

Certain cutaneous signs and symptoms of irritation and localized reactions at the application site such as erythema, scaling, dryness, stinging/burning, and pruritus may be experienced with use of CD5789. Depending upon the severity of these side effects, subjects may be instructed to reduce the frequency of application or to discontinue use.

Trifarotene cream contains propylene glycol that is mildly irritant to the skin, eyes, and mucous membranes. Trifarotene (CD5789) cream HE1 also contains butylated hydroxytoluene that may cause local skin reactions (e.g., contact dermatitis), or irritation to the eyes and mucous membranes and sodium benzoate that is mildly irritant to the skin, eyes, and mucous membranes.

CD 5789 is mildly irritant to the skin, eyes, and mucous membranes. Therefore, it should not come into contact with the eyes, mouth, or mucous membranes.

There is a potential risk of skin sensitization. If a reaction suggesting sensitivity to trifarotene (CD5789) cream HE1 occurs, the use of the trifarotene cream HE1 must be discontinued.

There is a potential risk of photosensitivity disorder (sunburn). Excessive exposure to sunlight or ultraviolet (UV) radiation (i.e., occupational exposure to the sun, planned holidays in the sun during the study, phototherapy, tanning salon) must be avoided during the studies. In addition, subjects should take protective measures such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet) and/or seeking shade or shelter from the sun.

As reported with other topical retinoids, there is a potential risk of pigmentation disorders.

No clinically significant systemic risks associated with CD5789 have been identified. Given the mechanism of action for CD5789 Cream HE1, it is assumed that efficacy will increase as the dose is increased. As such, the 200 µg/g dose was selected for the OLE based on its previously established safety profile, expected superiority to placebo and 100 µg/g. However the Data Safety Monitoring Board (DSMB), who will routinely review aggregate safety and tolerability data, as well as any safety concerns brought to the their attention by the study investigators or medical monitor, may determine that the study should be modified, placed on hold, or stopped if serious safety issues are discovered. This is applicable for both the double-blind portion and OLE. If the 200 µg/g dose in raises any safety concerns, the protocol will be amended and the dose will be reduced.

A summary of the pharmaceutical properties and known potential risks of trifarotene (CD5789) cream HE1 is provided in the current version of the investigator brochure (IB). The investigator must become familiar with all sections of the trifarotene (CD5789) cream IB before the start of the study.

6. OBJECTIVES

6.1. Primary Objective

The primary objective is to compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in adults and adolescents with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 90 days of treatment.

6.2. Secondary Objectives

The secondary objectives are as follows:

- To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% BSA twice weekly.
- To assess safety for up to 180 days of dosing with trifarotene cream HE1 200 µg/g.

7. STUDY DESIGN

7.1. Overall Study Design and Plan

The first part of this study is a phase 2, randomized, 2-cohort, double-blind, vehicle-controlled, multicenter study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in adults and adolescents with LI for 90 days. Adult and adolescent subjects who complete the randomized, double-blind, vehicle-controlled period of the study will be eligible to continue into an open-label extension (OLE) and be treated with trifarotene cream HE1 200 µg/g for an additional 90 days.

The randomized, double-blind, vehicle-controlled period of the study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Investigator Global Assessment [IGA] scale where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe), is designed to compare the safety of 2 doses of trifarotene cream HE1 with that of vehicle in the treatment of LI.

Written informed consent will be obtained from a parent/legal guardian for any minor and minors will provide assent before any study-related procedures are performed.

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods (Table 9-2), as applicable. Washout may be up to 90 days, as necessary.

During washout, subjects may continue taking their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard-of-care treatments in the electronic case report form (eCRF). If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower, but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline. After completing any necessary washout of prohibited medications, subjects will return to the site to have their LI assessed and to complete the study eligibility requirements.

Study drug will be packaged in 50-g tubes from which up to 36 g of IP may be dispensed per application, i.e., the maximum dose per application.

Study staff will choose 1 tube from the kit dispensed to the subject at that visit, and apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements; they will weigh the study tubebefore and after application to determine the amount used. If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.

The kit dispensed at baseline must be weighed before the first tube is chosen for application by the study staff. Weight of the kits dispensed and returned by the subject during the study includes both tubes and cartons, but not leaflets, which need to be removed before weighing. The subject must be reminded to return the kits with tubes and cartons, whether used or not, when returning to the next visit.

Thereafter, subjects will apply up to 36 g of study drug on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of IP in a tube.

The study protocol limits application of IP to 36 g maximum; no additional tubes can be given, whether during the randomization period or the OLE period. If the study staff and subject note that there is insufficient volume for full body application, the subject should apply trifarotene cream sparingly twice weekly to the most affected areas, and always to the same skin areas. Study cream should be very sparingly applied. Trifarotene cream 100 or 200 µg/g, is a highly potent topical retinoid and it is not necessary to apply much for efficacy; application of more will increase the risk of irritation and systemic penetration.

Enrolled subjects will receive treatment for 90 days.

The first cohort of subjects (Cohort A) will randomize adults (≥18 years old) in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle.

After the initial 15 subjects complete at least 28 days of treatment, an independent DSMB will review aggregate safety and tolerability data (including PK and electrocardiogram [ECG] data). If no safety issues are identified, adolescents (ages 12–17 years, inclusive) will be allowed to enroll together with adults in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and similarly treated twice weekly for 90 days in the same manner as subjects in Cohort A.

Cohort A will continue enrolling only adult subjects until the DSMB considers it safe to open recruitment in Cohort B.

All subjects will be given diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]), any application site reactions, adverse events (AEs), and concomitant medications used. Subjects will also be advised on permitted emollient(s) and/or sunscreen(s) use on nontreatment days during the study; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited.

At all sites with photographic capability photographs will be taken as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional, photographic informed consent form (ICF).

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit, as indicated in the Schedule of Events (Table 2-1). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have

remained in the skin after the last application. Subjects should not apply IP on visit days until after the visit.

In addition, a PK substudy will be conducted on Days 1 and 30 at sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 15 adults and 15 adolescents. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for all subjects at specified time points. For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30.

Efficacy will be assessed by the number of subjects in each treatment group who achieve "success" defined as clear/almost clear overall and at least a 50% reduction from Baseline at Day 90/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA scale (i.e., 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe). In addition, efficacy criteria include assessment scales for palm/sole, scaling, roughness, fissuring, and the Dermatology Life Quality Index (DLQI), and the EQ-5D Quality of Life (QoL) Questionnaire. Ectropion Severity Scores (ESS) between the active trifarotene cream HE1 and vehicle groups will be an exploratory endpoint.

Plasma concentrations of CD5789 and its major metabolites will be measured.

Safety will be assessed by evaluating reported AEs, changes in clinical laboratory test results, vital sign measurements, physical examinations, 12-lead ECGs, and local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]).

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent and/or assent through the post-treatment visit) will be documented.

Topical trifarotene cream HE1 was generally well tolerated in recently completed phase 3 pivotal and long-term safety studies in subjects aged 9 years and older with acne vulgaris. The local tolerability of the trifarotene cream HE1 formulation in subjects with LI is unknown and will be monitored during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. At each clinic visit, the investigator will assess local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]) on each treated body area (chest/abdomen, back, legs, arms, and face/neck).

All subjects who complete the Double-blind Treatment Period will be eligible to enroll in the OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly. During the OLE, subjects will return to the site at Days 104, 120, 150, 180, and 194. Additional PK samples will be drawn at Days 120 and 180 from all subjects who continue into the OLE (Table 2-2).

Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and AEs; see Section 9.4.

Figure 7-1: Double-blind Study Design

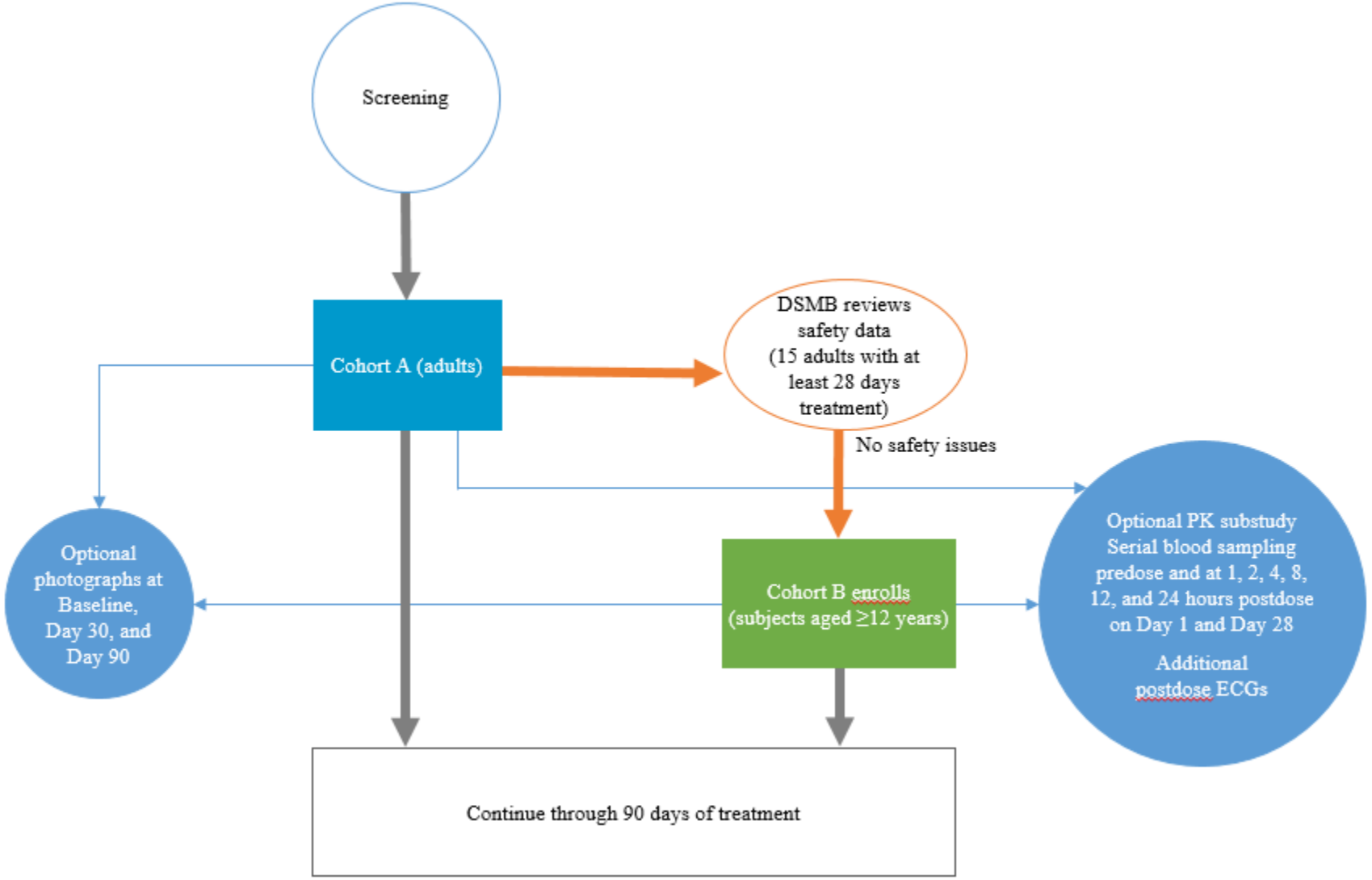
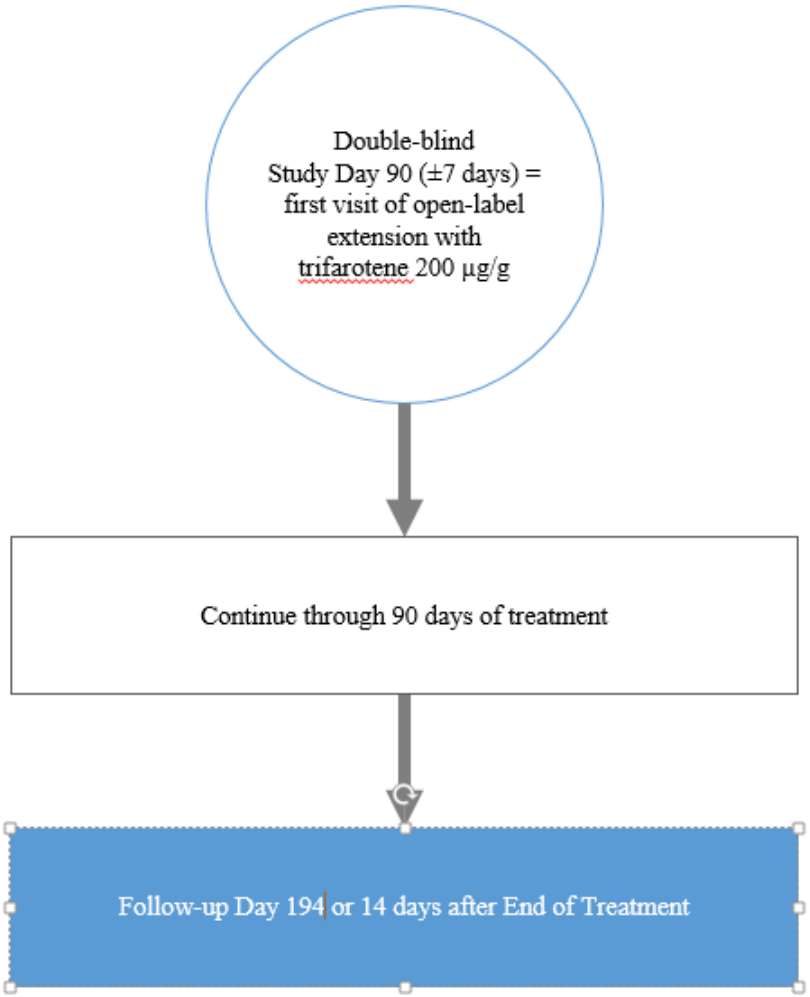


Figure 7-2: Open-label Study Design



7.2. Rationale and Discussion of Study Design

The first part of this study is a randomized, double-blind, placebo-controlled study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in adults and adolescents with LI.

In a previous proof-of-concept study (RD.03.SRE.40181E), subjects with LI applied trifarotene 50 and 100 µg/g cream to limited areas and results demonstrated a decrease in scaling with good safety and tolerance. In a phase 1 study in healthy Japanese and non-Japanese subjects (RD.03.SPR.103813), repeated topical applications of trifarotene (CD5789 cream HE1) 100 µg/g and 200 µg/g resulted in low and similar CD5789 systemic levels in all the cohorts. These studies are fully described in the current Investigational Brochure.

To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of adults randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly. An independent DSMB will review aggregate safety and tolerability data from the initial 15 subjects' first 28 days of treatment. If no safety issues are identified, adults and adolescents (ages 12–17 years, inclusive) will be allowed to enroll in Cohort B and randomized to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly in the same manner as subjects in Cohort A. All subjects in the randomized, double-blind portion of the study will be treated for 90 days and data on safety, tolerability, PK, and efficacy collected.

Adult and adolescent subjects who successfully complete the initial 90 days of double-blind treatment will have the option to enter an OLE with trifarotene cream HE1 200 ug/g twice weekly for 90 days.

The OLE will collect additional safety, tolerability, PK, and efficacy data. As designed, this study will provide important information on safety, tolerability, and PK with dosing of adolescents and adults with LI for up to 180 days.

The protocol includes appropriate monitoring for safety and tolerability. If subjects develop significant local application site reactions or tolerability issues, the protocol includes language for reducing the frequency of application or halting study drug application until the symptoms abate.

7.3. Selection of Doses in the Study

Based on the results from Study RD.03.SRE.40181E and Study SRE.103813, the doses of 100 µg/g and 200 µg/g were selected for further investigation in adult and adolescent subjects with moderate to severe LI to determine which of the 2 doses is most effective. The proof-of-concept (PoC) study demonstrated efficacious treatment with 100 µg/g in adults. The PK and tolerability study showed that, when the frequency of application was reduced from daily to twice weekly, the 200 µg/g cream HE1 had good local tolerability.

Therefore, the current study will use these doses compared with vehicle, applied twice weekly on up to approximately 90% BSA in subjects with LI. The OLE will evaluate the long-term safety of the higher dose in this patient population.

7.4. Study Sites

The study will take place at approximately 40 sites in North America, Europe, Israel, and Australia.

7.5. Point of Contact

A point of contact will be identified to provide information to subjects about where to obtain information on the study, the rights of subjects, and whom to contact in case of a study-related injury. This information will be provided in the subject information and informed consent form (ICF).

7.6. End of Study Definition

A clinical trial is considered completed when the last participant's last study visit has occurred.

8. SUBJECT POPULATION

8.1. Selection of Study Population and Diagnosis

Diagnosis of LI for the purposes of this study will be a clinical diagnosis. Although some younger subjects may have had genetic testing, older subjects may not.

While LI is a rare disease and subject enrollment may be challenging, due to possible bias introduced by including household members in the same study, it is recommended that only 1 household member be included in the study to maintain the blind and ensure all assessments are independent.

8.2. Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. For Cohort A: subject is ≥18 years old; for Cohort B: subject is ≥12 years old.
2. Subject has known diagnosis of LI.
3. Subject has moderate to severe (IGA 3–4) LI on the IGA of LI severity.
4. Subject has signed an ICF at Screening before any investigational procedures. Subjects <18 years of age (or Age of Majority) must sign an assent form in conjunction with an ICF signed by the parent/legal representative.
5. Subject who is participating in optional photography has signed a photography ICF.
6. Subject who is participating in the optional PK substudy has signed a PK ICF. Minors, in the event of their reaching majority during the study, should be capable of giving consent to take part in the PK substudy.
7. Subject is not of childbearing potential, who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason), or has documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   OR

- Subject is a woman of childbearing potential (WOCBP), i.e., a female ≥12 years of age (regardless of whether they have experienced/reported menarche), or a male subject with

sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception:

- bilateral tubal ligation
- combined oral contraceptives (estrogens and progesterone), vaginal ring, or implanted or injectable hormonal contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation
- intrauterine device (IUD) inserted at least 1 month before Baseline

OR

Agrees to abstain from heterosexual intercourse during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

AND

Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application.

Note: Female subjects who are premenstrual at screening should nonetheless follow the pregnancy testing schedule for WOCBP even if they abstain from sexual intercourse while in the study and for at least 1 month after the last study drug application.

8. Women of childbearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine).
9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent/assent, as applicable.
10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

8.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization, including syndromic ichthyoses.
2. Subject has current moderate or severe stinging/burning at Screening.
3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments.
4. Subject with fasting triglycerides >200 mg/dL or >2.25 mmol/L and/or total cholesterol >250 mg/dL or >6.5 mmol/L. Subjects whose triglycerides and/or total cholesterol are within normal limits with a stable dose of lipid-lowering agents for at least 6 months may be included.

5. Subject was previously treated with trifarotene/CD5789 in an acne or ichthyosis study.
6. Subject has any other significant concomitant disease, or poorly controlled medical condition other than LI that in the investigator's opinion may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis). Subjects with hypothyroidism who are on a stable dose of thyroid hormone replacement therapy and whose thyroid-stimulating hormone (TSH) is normal may be included
8. Subject is being treated for major depression disorder and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts.
9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening.
10. Subject with any of the following laboratory values at Screening:
    a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory
    b. Total bilirubin >1.25 × ULN at Screening. Subjects with known Gilbert's syndrome may be included with total bilirubin >1.25 × ULN
    c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women
    d. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L.
11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
12. Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment.
13. Subject has a history of long QT syndrome or has clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, or QTcF interval >450 ms.
14. Subject has a known allergy or sensitivity to any of the components of the investigational products.
15. Subject has been exposed to excessive UV radiations on the treated zones within 1 month before Baseline visit or is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.).
16. Subject is inherently sensitive to sunlight.
17. Subject is unable or unwilling to stop use of topical or systemic retinoids.
18. Subject is presumed to be abusing drug or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms.
19. Subject is participating in another interventional clinical trial.

20. Subject is institutionalized.

21. Subject is in any way related to the sponsor, investigator, or site personnel.

8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

8.4. Subject Discontinuation of Study Intervention and Stopping Rules

Subjects who discontinue the study treatment will be asked to return to the site to undergo ET procedures (see Section 10.2.4.6). If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

An investigator must discontinue a participant's study treatment for any of the following reasons:

- Pregnancy
- Significant study intervention noncompliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would result in a significant burden to the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for discontinuation of study treatment will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized, and receive the study intervention, and subsequently discontinue study treatment, or are withdrawn from the study will not be replaced.

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.5. Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Randomized subjects withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

9.1. Identification of Investigational Product

Trifarotene cream HE1 is a cream containing 100 or 200 µg/g (0.01% [w/w] or 0.02% [w/w], respectively) of CD5789 and the following excipients: purified water, propylene glycol, allantoin, glycerin, medium-chain triglycerides, polypropylene glycol 15 stearyl ether, cyclomethicone, phenoxyethanol, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane (simulgel 600 PHA), sodium benzoate, butylated hydroxytoluene, and gluconolactone. It is a potent RARγ agonist characterized by its high specificity to this receptor.

Sodium benzoate, butylhydroxytoluene, and propylene glycol are excipients known to have a recognized action or effect to be declared on the labeling, according to the CHMP Annex to the excipients in labeling and package leaflet of medicinal products for human use (EMA/CHMP/302620/2017). These 3 excipients are being used in the trifarotene formulation at standard concentrations and are all necessary to ensure adequate protection of the formulation along and the shelf life.

Vehicle contains the same ingredients, without the CD5789.

Trifarotene cream HE1 and vehicle will be provided in cream form for topical application and will be supplied in 50-g tubes from which a maximum of 36 g of IP may be extracted,

Trifarotene cream HE1 and vehicle will be supplied by G. Production, Inc. (Galderma) in Baie-D'Urfé, QC, Canada.

9.2. Treatments Administered

For the Double-blind Treatment Period, trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject. The IP should be applied thinly and gently rubbed in.

Study staff will apply the first administration of IP in the clinic on Day 1 after Baseline measurements, and the amount of IP used will be measured (i.e., 50-g tube will be measured before and after application to determine amount used). If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.

The maximum dose per application is 36 g (i.e., 1 tube). Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than full amount of product in a tube. Subjects will apply treatment for 90 days.

After the Day 1 visit, subjects will apply up to 36 g of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Persons other than the study subject applying the study drug must wash their hands after application or use disposable vinyl gloves. In addition, a long-handled applicator will be provided for application on the back. The applicator must be washed with warm water and soap after every application.

Trifarotene cream should not come into contact with the eyes, mouth, angles of the nose, or mucous membranes. For the ectropion treatment, Q-tips are recommended for precise application on eyelids, without contact to the eye or conjunctiva. If the IP gets into the eye, it must be flushed immediately with warm water. In case of eye irritation, the subject must be seen by an ophthalmologist.

For the OLE, all subjects will receive open-label trifarotene cream HE1 200 µg/g and apply it in the same manner as in the Double-blind Period for an additional 90 days.

Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application. Subjects should not apply IP on visit days until after the visit, unless they are participating in the PK substudy, in which case the IP will be applied in the clinic on Day 1 and Day 30 after the blood draw. Among subjects participating in the PK substudy, ensure the PK line is inserted before study drug application to prevent contamination with the IP and to protect the skin around the needle insertion point from study drug application.

9.3. Selection of Timing of Dose for Each Subject

Subjects will be randomized in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week, 3 to 4 days apart on which to apply their IP and maintain that regimen each week throughout the study (Table 9-1). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained on the skin after the last application. Subjects whose treatment day falls on a scheduled study visit day should not apply the IP until after the visit.

Subjects who participate in the PK substudy should have their Day 30 Visit scheduled on a treatment day, in which case the IP will be applied in the clinic on Day 30 after the predose PK blood draw. If the Day 30 Visit cannot be scheduled on a treatment day, the investigator should contact the medical monitor.

All subjects will be provided with diaries in which to record study drug application (days/times) and any areas of skin not treated (e.g., due to local reactions).

If a subject misses an IP application, they should apply the IP as soon as they remember and record the date/time in the subject diary. The next application should be 3 to 4 days apart, and subjects should continue according to their new regimen.

Subjects should not shower, bathe, or swim for at least 4 hours after IP application. No occlusive dressings should be used on areas to which IP is applied.

Subjects who continue into the OLE will receive trifarotene cream HE1 200 µg/g and apply it in the same manner as in the Double-blind Period for 90 days.

Table 9-1: Sample Twice-weekly Dosing Schedule

	Week 1							Subsequent Weeks						
	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Option 1	X			X				X			X			
Option 2		X			X				X			X		
Option 3			X			X				X			X	
Option 4				X			X				X			X
Option 5	X				X			X				X		
Option 6		X				X			X				X	
Option 7			X				X			X				X

9.4. Dose Adjustment Criteria

Local tolerance will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]) for each treated body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed:

- If a score of 2 (moderate) is recorded for any of the local tolerability assessment scales (stinging/burning, pruritus or erythema) on any treated area (e.g., the face), the study drug will be applied on this area only once weekly, until the score returns to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas.
- If a score of 3 (severe) is recorded any of the local tolerability assessment scales (stinging/burning, pruritus or erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas.

Any changes in dosing must be documented in the subject diary and the eCRF.

9.5. Treatment Compliance

Subjects will be asked to record their twice-weekly applications of IP in the diary during both the Double-blind Period and the OLE. Deviations from the planned doses (missed dose or timing) will be recorded on the subject's eCRF. Study personnel will review diaries at each visit and diaries will be collected as source documents. Information from subject diaries will be transcribed on the appropriate eCRF pages for documentation of subject compliance with the IP.

Study personnel will assess treatment compliance with IP regimens by weighing kits (tubes and boxes, but not leaflets) before dispensing and upon return and by questioning the subject, at every postrandomization visit. At baseline, the kit should be weighed before choosing the first tube for application by the study staff. A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, supplemented by amount of cream used derived from weighing the IP kits. A subject who is not compliant (for example, used 80–120% of IP tubes [which is more than what can be dispensed per tube at each application]) will be counseled at each visit on the importance of using the IP as instructed.

Subjects who taper to once-weekly application or who take a "drug holiday" for tolerability will not be reported as having deviated from the protocol (see Section 9.4 for dose adjustment and stopping rules); any changes in dosing must be documented in the subject diary and the eCRF.

9.6. Method of Assigning Subjects to Treatment Groups

In the double-blind, parallel-group, randomized period of the study, subjects who meet study entry criteria will be randomly assigned in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. Study center will not be a blocking factor in the randomization schedule.

Premier Research will prepare the randomization schedule before the start of the study. No one involved in the study performance will have access to the randomization schedule before the official unblinding of treatment assignments. No subject will be randomized into this study more than once.

In the OLE, all subjects will receive trifarotene cream HE1 200 µg/g.

9.7. Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the Double-blind Period of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician and programmer from Premier Research who will have access to the randomization code. The statistician will have access to unblinded data if there is an unblinded DSMB review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

The investigator may discuss with the medical monitor in advance of unblinding a subject, if possible, if it is not deemed an emergency. However, the investigator has the ultimate decision for unblinding a subject for medical treatment and no procedures will prevent or delay necessary unblinding in an emergency for the subject's safety. For emergency unblinding, study personnel will use the IWRS code. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

The primary analysis period is the first 90 days of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after database lock has been achieved. A second analysis will take place for endpoints assessed from Day 90 through the OLE.

9.8. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

Upon signing informed consent and entering the Screening Period, subjects may begin a Washout Period of up to 90 days. Participants will stop using physical and medical treatments for LI,

including balneotherapy, as well as the following prohibited medications, as applicable (Table 9-2).

Table 9-2: Washout Periods for Prohibited Medications[a]

Medication	Washout Period
Topical Treatments	
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogs	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	2 weeks
Systemic treatments	
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones unless the dose is stable and TSH is normal, cytotoxics, bisphosphonates, selective estrogen receptor modulators (SERM), teriparatide, calcitonins, tetracyclines, quinolones, thiazides, long-term use of salicylates, heparin, theophylline, barbiturates, colchicines. Vitamin D analogs taken at stable dose for at least 1 month are allowed	8 weeks
QT-prolonging drugs	5 half lives
CYP Enzyme inducers (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (including, but not limited to the following: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives
Monoclonal antibodies	5 half lives

a Note: This list applies to both prescription and over-the-counter (OTC) medications

During washout, subjects may continue their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard-of-care treatments in the eCRF. If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower, but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.

After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.

9.8.1 Permitted Therapies

Subjects will be advised on permitted emollient(s) for use as often as needed on nontreatment days during the study; on treatment days, the use of emollient(s) is permitted except within 4 hours

before or after study drug application. Similarly, protective sunscreen should be applied as often as needed, except within 4 hours before or after study drug application. Subjects may use their standard of care treatment on their faces and/or palms/soles after the Day 30 assessment if they experience a worsening of IGA in those areas. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. These standard of care treatments should be approved by the investigator and documented in the eCRF.

Subjects who enter the OLE must stop standard of care treatment. If they experience a worsening of IGA they may use standard of care treatment on their faces and/or palms/soles after the Day 120 Visit if the standard of care does not contain prohibited medications. If those standard of care treatments include prohibited medications, the subject should be discontinued from the study.

Other concomitant medications are allowed (e.g., analgesics, antihistamines), but should be limited to those medications considered necessary. All concomitant medications, both prescribed and over-the-counter, should be recorded in the eCRF.

9.8.2 Prohibited Therapies

The medications listed in Table 9-2 are prohibited during the study. Balneotherapy is also prohibited during the Screening Period and during the study.

Subjects may not use concomitant keratolytics such as urea, salicylic acid, alpha, or beta hydroxyacids. Subjects may not use topical or systemic retinoids. Subjects may not take more than 3500 IU/day Vitamin A (e.g., as in a multivitamin). Use of benzoyl peroxide is permitted on nontreatment days for subjects with concomitant acne only); it must not be applied on treatment days due to risk of inactivation of trifarotene by benzoyl peroxide.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continued treatment in the study, at the investigator's discretion with consultation with Mayne Pharma LLC and the medical monitor. For enrolled subjects who require prescription of a systemic azole, the principal investigator should discuss with the medical monitor whether the subject may continue in the study.

9.8.3 Restrictions

Subjects should not shower, bathe, or swim for at least 4 hours after study drug application. No occlusive dressings should be applied to areas where study drug was applied.

Subjects should only use investigator-approved emollients, and should not use them on treatment days within at least 4 hours before and after study drug application.

In addition, subjects should take protective measures to avoid exposure of treated areas to sunlight, such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet), and/or seeking shade or shelter from the sun.

9.9. Treatment after End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.10. Dispensing and Storage

The test product supplied by Mayne Pharma LLC is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Premier Research. Until the IP is dispensed to the subjects, it must be stored at 20–25°C (68–77°F), with excursions permitted to 15–30°C (59–86°F); do not freeze and with the tube kept tightly closed in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

9.11. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of subjects (subject number) who received the IP. The investigator will not supply the IP to any person except those named as subinvestigators on the Form Food and Drug Administration (FDA) 1572, designated study personnel, and subjects in this study. The investigator will not dispense the IP from any study sites other than those listed on the Form FDA 1572. Investigational product(s) may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Each subject will be given enough tubes of study drug to apply up to 1 tube-full (approximately 36 g of clinical trial material) per treatment day until the next study visit. Tubes will be packed 2 to a carton, and each subject will receive enough cartons to have the maximum number of tubes needed until the next study visit. The number of study drug tubes the subject needs to provide enough IP until the next visit is shown in Table 9-3.

Table 9-3: Amount of Study Drug Needed Per Visit

Treatment Period	Number of Cartons	Number of Tubes
Double-blind Treatment Period		
Baseline	3	6
Day 14	4	8
Day 30	6	12
Day 60	6	12
OLE		
Day 90	3	6
Day 104	4	8
Day 120	6	12
Day 150	6	12

Each carton will be weighed before dispensing (tubes and boxes, but not leaflets) and subjects are to bring all cartons and tubes back at each study visit, whereupon study staff will weigh them again to estimate study drug use and compliance.

Upon completion of the study, the IP (partly used, unused, and empty tubes) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.12. Labeling and Packaging

Labeling and packaging of IP will be performed by Catalent Pharma Solutions.

Tubes will be packaged in cartons comprising 2 tubes each. Tubes will be labeled with inner and outer booklet labels, and carton number. Each carton will also be labeled with inner and outer booklet labels and numbered.

9.12.1 Labeling

The tubes will have a label affixed that meets the applicable regulatory requirements and may include, but is not limited to, the following: subject identifier, IP name, lot number, protocol number, carton number, caution statement, storage, and sponsor identification.

All empty packaging or packaging containing unused tubes should be saved for final disposition by the sponsor or contract pharmacy.

Final labeling will comply with the regulatory requirements of each country where the study will be conducted.

9.12.2 Packaging

Investigational products will be packaged in high-density polyethylene, 35×100 mm tubes weighing 50 g from which a maximum of 36 g of IP can be extracted. Trifarotene cream HE1 and vehicle will be packaged so as to be blinded to the investigator, the study clinic personnel, and the subjects.

10. STUDY PROCEDURES

Subjects must provide written informed consent and/or assent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy. Written informed consent will be obtained from a parent/legal guardian for any minor and minors will provide assent before any study-related procedures are performed.

Subjects who agree to participate in the photography and/or PK substudy must provide written informed consent before photographs or serial blood samples are collected.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

10.1.1 Overall Study Schedule

The planned sequence and maximum duration of the study periods for each subject will be as follows:

1. Screening: up to 97 days. Before asking a subject to enter washout, investigators should confirm the subject meets study eligibility criteria, except for LI severity (inclusion criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined.
2. Double-blind treatment: Twice weekly for 90 days.
3. Optional Open-label Extension treatment: Twice weekly for 90 days.
4. Follow-up: 14 days after last study drug application.

The maximum treatment duration for each subject is approximately 90 days for subjects who choose not to continue into the OLE, and 180 days for those who choose to continue.

The maximum study duration for each subject is approximately 291 days.

10.2. Study Periods and Visits

It is suggested that quality of life assessments be conducted first to avoid any bias, and that the IGA be recorded as the first LI assessment at every visit.

10.2.1 Screening and Washout

10.2.1.1 Screening Visit (Visit 1)

Written informed consent must be obtained before any study-related procedures are performed. Before asking a subject to enter Washout (Section 10.2.1.1.1), investigators should confirm the subject meets study eligibility criteria, except for LI severity (Inclusion Criterion #3). Washout may be up to 90 days. After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and study eligibility requirements determined.

The following procedures will be performed during Screening:

1. Obtain written informed consent and/or assent.
2. Assign a screening number when a subject begins screening.
3. Assess inclusion/exclusion criteria.
4. Collect demographic information.
5. Record medical history, including current therapies (e.g., prescription and nonprescription medications).
6. Perform a physical examination.

7. Measure vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse).
8. Measure height, weight, and calculate body mass index (BMI).
9. Record IGA.
10. Record VIIS.
11. Record roughness assessment.
12. Record palm/sole assessment.
13. Record palm/sole assessment of fissuring.
14. Record ectropion score.
15. Perform a 12-lead ECG
16. Collect blood and urine for laboratory tests, coagulation panel, and serology.
17. Perform serum pregnancy test for WOCBP.
18. Record concomitant medications.

Procedures for rescreening subjects who initially fail to meet study entry criteria are described in Section 14.3.

10.2.1.1.1 Washout

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and begin to washout the prohibited topical and systemic treatments with designated washout periods, as applicable (Table 9-2). Washout may be up to 90 days, as necessary.

After completing any necessary Washout Period, subjects must return to the site within 35 days before the Baseline Visit within the 97-day Screening Period to have their LI severity assessed and to complete any eligibility requirements. During washout, subjects may continue their standard of care of visible skin (face and scalp) for cosmetic reasons and of extremities (palms/soles) to avoid functional consequences on walking or moving their fingers. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. The investigator should approve and document these standard-of-care treatments in the eCRF. If the standard of care treatments of the face and/or palms/soles contain prohibited medications, they must be stopped at the Baseline Visit. Subjects may shower but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.

10.2.2 Double-blind Treatment Period

Eligible subjects who have washed out prohibited medications will be randomized to double-blind study drug.

10.2.2.1 Baseline Visit (Visit 2, Day 1)

The following procedures will be performed on Day 1 in the study clinic:

1. Review inclusion/exclusion criteria.

2. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.5 and 10.3.1.6 for which version of questionnaire to use).
3. Perform a limited physical examination.
4. Record vital signs (blood pressure and pulse).
5. Record concomitant medications and concomitant therapies.
6. Record IGA.
7. Record VIIS.
8. Record roughness assessment.
9. Record palm/sole assessment.
10. Record palm/sole assessment of fissuring.
11. Record ectropion score.
12. At sites where the photographic substudy is conducted, take photographs of subjects who have provided informed consent for the photography.
13. Perform a 12-lead ECG.
14. Perform urine pregnancy test for WOCBP.
15. Collect blood and urine for routine laboratory tests (subject must be fasting; i.e., at least 8 hours) and coagulation panel.
16. Randomize via IWRS.
17. Collect a predose PK blood sample (all subjects).
18. Among subjects who consent to participate in the PK substudy, ensure that PK lines are placed before IP application. The IP will be applied in the clinic at this visit, and samples for PK will be taken at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1.
19. Among subjects in the PK substudy, perform additional ECGs at times of serial sampling.
20. Clinic staff instructs subject on study drug application, applies initial study drug dose and measures amount used (i.e., study staff will weigh the kits (tubes and boxes, but not leaflets)before and after the first application. If the product will be applied at home by someone other than the study subject, it is recommended that person assists with application at this visit to learn how the IP is applied.
21. Assess and record local tolerance/AEs.
22. Dispense study drug and diaries.
23. Advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that at least 24 hours must have elapsed since IP application before their next visit. Subjects should not to apply IP on visit days until after the visit.

10.2.2.2 Telephone Visit (Day 7)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited), and remind subjects that at least 24 hours must have elapsed since IP application before their next visit. Subjects should not apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.2.3 Visit 3 (Day 14 ±5 days)

The following procedures will be performed on Day 14 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.6 and 10.3.1.7 for which version of questionnaire to use).
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Record IGA.
5. Record VIIS.
6. Record roughness assessment.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring
9. Record ectropion score.
10. Assess local tolerance.
11. Record AEs and review diary.
12. Collect a PK blood sample (all subjects).
13. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
14. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.
15. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.

10.2.2.4 Visit 4 (Day 30 ±7 days)

The following procedures will be performed on Day 30 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.6 and 10.3.1.7 for which version of questionnaire to use).
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Record IGA.
5. Record VIIS.
6. Record roughness assessment.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring
9. Record ectropion score.
10. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
11. Assess local tolerance.
12. Record AEs and review diary.
16. Perform a 12-lead ECG
17. Perform a urine pregnancy test for WOCBP.
18. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours) and coagulation panel.
19. Collect a PK blood sample (all subjects).
20. Among subjects who consent to participate in the PK substudy, ensure that PK lines are placed before IP application. The IP will be applied in the clinic at this visit, and samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose.
21. Among subjects in the PK substudy, perform an additional ECGs at times of serial sampling.
22. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
23. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before and after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.
24. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.
25. Provide information about OLE option to study subject.

10.2.2.5 Telephone Visit (Day 45)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited), and remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary. Staff will remind subject about OLE option.

10.2.2.6 Visit 5 (Day 60 ±7 days)

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.6 and 10.3.1.7 for which version of questionnaire to use).
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Perform a urine pregnancy test for WOCBP.
5. Record IGA.
6. Record VIIS.
7. Record roughness assessment.
8. Record palm/sole assessment.
9. Record palm/sole assessment of fissuring
10. Record ectropion score.
11. Assess local tolerance.
12. Record AEs and review diary.
13. Collect a PK blood sample (all subjects).
14. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
15. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before and after study drug application is prohibited. Remind subjects that Added reminder that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.
17. Provide information about OLE option.

10.2.2.7 Visit 6 (Day 90 ±7 days) or Early Termination

The following procedures will be performed on Day 90 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.6 and 10.3.1.7 for which version of questionnaire to use).
2. Perform a limited physical examination.
3. Record vital signs (blood pressure and pulse).
4. Record concomitant medications and concomitant therapies.
5. Record IGA.
6. Record VIIS.
7. Record roughness assessment.
8. Record palm/sole assessment.
9. Record palm/sole assessment of fissuring.
10. Record ectropion score.
11. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
12. Assess local tolerance.
13. Record AEs and review diary.
14. Perform a 12-lead ECG.
15. Perform a urine pregnancy test for WOCBP.
16. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours) and coagulation panel.
17. Collect a PK blood sample (all subjects).
18. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.

For subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 90 days of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing, PK from Day 90 will be carried over to the OLE and will not be repeated. If the subject chooses to continue into OLE, the following additional procedures will be done:

1. Have the subject sign OLE-specific informed consent.
2. Measure subject's weight.
3. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that at least 24 hours must have elapsed since IP application before the

PK draws at the Day 120 and Day 180 Visits, and not to apply IP on visit days until after the visits.

4. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit (only for subjects who choose to continue into the OLE).
5. Dispense study diary.

10.2.3 Follow-up Telephone Call (±14 days after Day 90) – Only Subjects Who Do Not Continue into Open-label Extension

Clinic staff will telephone subjects who choose not to continue into the Open-label Extension within 14 days after Day 90 to assess any ongoing AEs.

10.2.4 Open-label Extension

Subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 90 days of double-blind treatment may choose to continue into an optional 90-day OLE with trifarotene cream HE1 200 µg/g. During the OLE, subjects will return to the site at Days 104, 120, 150, 180, and 194. Additional PK samples will be drawn at Days 120 and 180 from all subjects who continue into the OLE.

10.2.4.1 Telephone Visit (Day 97)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and to remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.2 Visit 7 (Day 104 ±5 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.

11. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.
12. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit (Day 120), and if the Day 120 visit coincides with a treatment day, wait until after the visit is complete to apply IP.

10.2.4.3 Visit 8 (Day 120 ±7 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Perform a 12-lead ECG.
11. Perform a urine pregnancy test for WOCBP.
12. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours) and coagulation panel.
13. Collect a PK blood sample (all subjects)
14. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
15. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited.

10.2.4.4 Telephone Visit (Day 134)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited),

and to remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.5 Visit 9 (Day 150 ±7 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Perform a urine pregnancy test for WOCBP.
11. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.
12. Weigh new study drug kits (tubes and boxes, but not leaflets) and dispense enough additional study drug until next visit, and new diary.
13. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit (Day 180) and if the Day 180 visit coincides with a treatment day, wait until after the visit is complete to apply IP.

10.2.4.6 Visit 10 (Day 180 ±7 days) or Early Termination

The following procedures will be performed at this study clinic visit:

1. Perform a physical examination.
2. Record vital signs (blood pressure and pulse).
3. Record concomitant medications and concomitant therapies.
4. Record IGA.
5. Record VIIS.
6. Assess roughness.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring.
9. Record ectropion score.
10. Assess local tolerance

11. Record AEs and review diary.
12. Perform a 12-lead ECG.
13. Perform a urine pregnancy test for WOCBP.
14. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours) and coagulation panel.
15. Collect a PK blood sample (all subjects)
16. Collect returned study drug tubes; confirm study drug compliance by weighing returned kits (tubes and boxes, but not leaflets) and reviewing diaries.

10.2.4.7 Follow-up Evaluation – Open-Label Extension (Day 194 or 14 days after End of Open label Treatment /Visit 11)

At 14 days after the last administration of the IP, the following procedures will be performed:

1. Perform a limited physical examination.
2. Record vital signs (blood pressure and pulse).
3. Record any concomitant medications/therapies.
4. Record IGA.
5. Record VIIS.
6. Assess roughness.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring.
9. Record ectropion score.
10. Assess and record AEs occurring since the last evaluation and review diary.
11. Perform a urine pregnancy test for WOCBP.

10.3. Assessments

The 5-point IGA is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. The IGA scale was developed with the support of experts from academic reference centers for the treatment of ichthyosis. Each level of severity will consider both the severity of scaling and the severity of roughness (Section 10.3.1.2). While retinoid treatment is expected to reduce scale, it may increase erythema; therefore, in this study, erythema will be evaluated as part of local tolerability.

10.3.1 Efficacy Variables

All efficacy measurements will use scales previously used for dermatological studies or as defined in the following sections.

10.3.1.1 Investigator's Global Assessment

The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear and at least a 2-grade change from Baseline at Day 90/EOT in the Double-blind Period on a 5-point IGA full body scale.

The investigator will rate the subject's condition using the 5-point IGA at each time point shown in the Schedule of Events (Section 2.2).

The IGA will be measured on a 5-point scale, excluding the following areas: knees, elbows, neck, palms, soles, axillae, groin, and scalp:

0	Clear	No scaling and no roughness
1	Almost Clear	Occasional fine scales; hardly palpable roughness (mostly smooth)
2	Mild	Small and fine scales predominate; no more than a few large scales; mild roughness on palpation
3	Moderate	Some large scales that may be thick,; coarse roughness on palpation
4	Severe	Confluent, primarily large (>1 cm), thick scales with plate-like hyperkeratosis

10.3.1.2 Visual Index for Ichthyosis Severity – Scaling

The secondary endpoint is the number of subjects in each treatment group who experience a severity score of 0 or 1 at Day 90/EOT on the overall 16-point VIIS for scaling.

The investigator will rate the subject's condition using the 5-point VIIS for each body area (chest/abdomen, back, legs, and arms) and an overall score at each time point shown in the Schedule of Events (Section 2.2):

0	Normal skin; no perceptible scale or smoothening
1	Areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
2	Confluent smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
3	Confluent scales (visibly separated/fractured stratum corneum) including some large (>1 cm), thick scales
4	Confluent, primarily large, thick scales

10.3.1.3 Individual Score for Roughness

The amount of roughness of the skin overall will be measured on a 5-point scale.

0	Clear	Smooth skin
1	Almost Clear	Hardly palpable roughness
2	Mild	Mild roughness (fine sand paper-like)
3	Moderate	Moderate, coarse roughness (coarse sand paper-like)
4	Severe	Very coarse skin (broken cornflakes-like)

10.3.1.4 Palm/Sole Assessment

Thickening of the skin on the palms and soles will be measured on a 5-point scale.

0	Clear	No thickening, no roughness, no fissure
1	Almost Clear	Only slight thickening, minimal to no roughness, no fissures
2	Mild	Some thickening, mild roughness on palpation, few fissures may be present
3	Moderate	Substantial and diffuse thickening, coarse roughness on palpation may be present, fissures may be present
4	Severe	Very thickened and rough skin, numerous fissures

10.3.1.5 Palm/Sole Fissuring Assessment

Fissuring will be assessed by recording the presence or absence of fissures, the number of fissures present, and the pain associated with each fissure. A fissure is a longitudinal and deep crack that separates the stratum corneum and may penetrate down to the dermis, causing pain and sometimes bleeding. The subject will assess pain associated with fissures as ranging from 0-3 (none, mild, moderate, severe).

10.3.1.6 Dermatology Life Quality Index

The DLQI is a dermatology-specific Quality of Life instrument for subjects aged 17 years and older (1992). The child DLQI (cDLQI; May 1993) is for subjects aged 12 to 16 years. It is a simple 10-question validated questionnaire with 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment); higher scores indicate poorer quality of life. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The investigator should use his or her judgment of the maturity of the subject to decide which version of the questionnaire to use; the same version must be used for the subject throughout the study.

10.3.1.7 EQ-5D Quality of Life Questionnaires

The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS). The EQ-5D-5L (2009) is intended for use in adult subjects, while the EQ-5D-Y (2012) is to be used for children and adolescents. The

investigator should use his or her judgment of the maturity of the subject to decide which version of the EQ-5D to use; the same version must be used for the subject throughout the study.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the subject's self-rated health on a vertical 0-100 VAS. This can be used as a quantitative measure of health outcome that reflects the subject's own judgment.

10.3.1.8 Ectropion Severity Score

The ESS, has a maximum score of 8 points. A higher score indicates a worse ectropion. The score takes the severity of ectropion in terms of lateral and medial apposition, scleral show, conjunctival show, and roundness of the eye into account and gives an indication of the functional aspects involved in ectropion by scoring redness, excess tear film, and the position of the lacrimal punctum.[14]

Table 10-1: Ectropion Severity Score

	Points per Item		
	0	**0.5**	**1**
Lateral apposition	Nonaffected	—	Affected
Medial apposition	Nonaffected	—	Affected
Scleral show	No	≤1 mm	>1 mm
Conjunctival show	No	—	Yes
Excess tear film	No	—	Yes
Redness of the eye	No	—	Yes
Round canthus	No	—	Yes
Punctum lacrimale	Invisible	Emerging	Visible
Maximum score			8 points

Source: Korteweg SFS, Stenekes MW, van Zyl FE, Werker PMN. Paralytic Ectropion treatment with lateral periosteal flap canthoplasty and introduction of the ectropion severity score. *Plast Reconstr Surg Glob Open.* 2014;2(5):e151.

10.3.1.9 Photography Substudy

All sites that have photographic capability will take photographs as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional photographic informed consent form (ICF).

10.3.2 Clinical Pharmacology

10.3.2.1 Pharmacokinetic Analysis Methods

The pharmacokinetic characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis (NCA).

10.3.2.2 Pharmacokinetic Parameters

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit for trough values.

Subjects who provide written informed consent to participate in the optional PK substudy will provide blood samples for PK analysis predose on Day 1 and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30.

The PK parameter estimates will be completed using WinNonlin (Pharsight Corporation) software using the actual elapsed times from dose administration to sample collection (i.e., not nominal time).

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the maximum concentration (C_{max}) and the time of C_{max} (T_{max}). Additional details of the parameters and their calculation and evaluation will be included in the statistical analysis plan (SAP).

Table 10-2 shows the PK parameters that will be computed for each subject for samples obtained over the planned sampling intervals.

Table 10-2: Pharmacokinetic Parameters

Parameter	Description of Parameter
C_{max}	Maximum (or peak) serum concentration
T_{max}	Time at which C_{max} is observed
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration-time curve from time 0 to infinity (if data permits)
$t_{1/2}$	Apparent first order terminal elimination half-life
λ_z	Apparent terminal phase rate constant (if data permits)

10.3.3 Sample Collection

Samples will be collected at the time points specified in the Schedule of Events (Section 2.2). Specimen preparation, handling, shipment, and storage for the complete blood count, chemistry, and urinalysis are described in the study laboratory manual. Finding veins in subjects with this disease can be challenging. Blood draws will be done at the corresponding study visits before application of the IP and should be 24 hours after IP application. Subjects must not apply the IP to the area where blood will be drawn within 24 hours before their next study visit to avoid contamination of the blood by IP that remained in the skin. For subjects in the PK substudy, a cannula should be placed before IP application and the cannula site may be occluded to prevent contamination with IP.

Actual PK sample times for subjects in the PK substudy will be recorded in the eCRF.

Blood

For subjects not in PK substudy:

The expected amount of blood to be drawn at each visit varies from approximately 6 mL to a maximum of 21 mL (Screening Visit only). The total amount of blood drawn for the study will be about 123 mL per subject, unless the subject takes part in the PK substudy.

For subjects in PK substudy:

For subjects who opt to participate in the PK substudy, extra blood samples will be drawn at Visit 2 and at Visit 4 for PK analysis. The amount of blood to be drawn per subject at each of these visits will be approximately 54 mL. For subjects taking part in the substudy, the total amount of blood drawn for the entire study will be approximately 195 mL.

Urine

Urinalysis will be performed at central laboratory. Dipstick and urine pregnancy tests will be conducted on site.

10.3.4 Safety Variables

Safety assessments will include the evaluation of AEs, including local tolerability (stinging/burning, pruritus, and erythema), clinical laboratory assessments, vital signs, 12-lead ECGs, and physical examinations.

10.3.4.1 Clinical Laboratory Safety Assessments

10.3.4.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 2.2).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides
Coagulation Panel:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones
Pregnancy Test:	for women of childbearing potential only; serum at Screening, urine at each other visit.
Serology	Hepatitis B surface antigen, and hepatitis C

All blood samples for the clinical laboratory tests must be taken in a fasting state, at least 8 hours after the previous drug application.

Blood and urine samples for hematology, and serum chemistry will be sent to a central laboratory for analysis. Urine pregnancy tests and dipstick will be conducted at the study sites.

10.3.4.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

Samples for assessment of clinical laboratory tests will be transported to the Clinical Reference Laboratory (see the study laboratory manual for addresses).

10.3.4.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Mayne Pharma LLC prior to beginning the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically significant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical significance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically significant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.4.2 Clinical Examinations

10.3.4.2.1 Vital Signs

Vital signs, including height and weight (only assessed at Screening), blood pressure, and pulse will be measured.

10.3.4.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. All ECG recordings will be identified with the subject number, date, and time of the recording. Gel ECG electrodes may be used for ECGs because they are more conductive and cause less trauma on compromised skin. Efficacy assessments should be conducted before ECGs to avoid possible artifact/changes from the ECG.

For subjects in the PK substudy, additional ECGs will be performed postdose during serial blood sampling on Day 1 and Day 30.

If there is a marked prolongation of the QT/QTc interval during treatment, a subject should be discontinued from the IP but remain in the study until full resolution of the event. The DSMB will be informed immediately of such an occurrence.

10.3.4.2.3 Physical Examination

A complete physical examination excluding the genitourinary examination will be performed at Screening, while limited physical examinations (to include HEENT, cardiorespiratory, abdomen, and range of motion) will be performed as indicated in the Schedule of Events (Section 2.2).

10.3.4.2.4 Other Safety Variables

Local tolerability will be assessed on a 0-3 scale (none, mild, moderate, severe). All application site reactions will be recorded as TEAEs in the diary. These should include the date and severity of the TEAE.

10.3.4.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

10.4. Procedural Adjustments Due to COVID-19

The coronavirus (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted to control the spread of the disease. It is recommended that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19.

Although it is preferable to conduct all necessary study assessments in person (onsite visits), this may not be possible as a result of COVID-19-related travel restrictions. To ensure the safety of subjects, investigators, and site staff, Visits 3-6 (Double-blind Period; Table 2-1), Visits 7-11 (OLE Period; Table 2-2) and unscheduled visits may be conducted remotely. Screening and baseline visits must be performed onsite only, and must be postponed or scheduled for when onsite visits can be safely conducted.

Appendix B details the procedures when it is inadvisable or not possible to conduct an onsite study visit.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in subjects treated with control product are also considered AEs.

11.1.2 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADRs).

The phrase “responses to an investigational product” means that a causal relationship between an investigational product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IP qualify as ADRs.

All AEs for which the judgment of relationship to IP is “possible” or higher will be considered ADRs. If a relationship to IP is not provided, then the AE must be treated as if it were “possible.”

11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For a preapproval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure [IB] for an unapproved investigational product or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis.

Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events.

11.1.4 Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first application of IP (trifarotene or vehicle) and not more than 14 days after the last application of IP.

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review by a study monitor.

All reported AEs, including local and systemic AEs not meeting the criteria for SAEs, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All reported AEs occurring while on study must be documented appropriately regardless of relationship. All reported AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of a reported AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study clinic personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 14 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs. In addition, although local tolerability will be assessed on a 0-3 scale, all application site reactions should be recorded as AEs.

The Tolerability Assessments Form at each visit collects a numeric severity score by body area for erythema, stinging/burning, and pruritus.

In addition, if skin irritation is more than the expected erythema, stinging/burning, and pruritus with the application of this topical retinoid (i.e., clinically relevant), please enter the application site reactions in the Adverse Event description section. If a diagnosis is known, record the diagnosis. If a diagnosis is known and there are other signs/symptoms that are not generally part of the main diagnosis, record the diagnosis and each sign/symptom on a separate line. If a diagnosis is not known, record each sign/symptom on a separate line. Examples are allergic contact dermatitis, sunburn, skin erosion, and swelling.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as follows:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3 Action(s) Taken

All AEs will be treated/managed according to standard practice. The following actions may be taken with regard to the IP. Section 9.4 describes dose adjustment and stopping rules for individual subjects.

Action(s) taken may consist of the following:

Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by reducing the frequency of application.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome of an AE at the time of last observation will be classified as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to IP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related	An AE with a reasonable time sequence to administration of the IP, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Related	An AE occurring in a causal plausible time relationship to IP administration that cannot be attributed to a concurrent disease or other drugs, chemicals, or events. The AE relationship to the IP must be assessed separately by the investigator and Mayne Pharma LLC.

11.2.3 Documentation

Any AE that occurs during the Screening Period will be captured as on the AE page of the eCRF (not medical history). All AEs that occur within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)

- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP(s)

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject may be withdrawn for treatment but continue to be followed for efficacy and safety in the study. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

It is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

Any AE will be followed (up to a maximum of 14 days after the last dose of IP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to Premier Research within 24 hours of first becoming aware of the event by e.g., completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the Premier Research by one of the following methods:

Email: globalPV-US@premier-research.com

Email: PVDS-ROW@premier-research.com

Fax number: +1 215 972 8765

Fax number: +421 2 6820 3713

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of IP(s)
- Date of last dose of IP(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s) ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, adverse event, date of occurrence, subject identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the Premier Research Pharmacovigilance Department using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB)/independent ethics committee (IEC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.2 Adverse Drug Reactions

All ADRs should be reported by the investigator in the eCRF.

Suspected serious ADRs must be reported to the sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.3 Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported by Premier Research to Mayne Pharma LLC in aggregate monthly status reports.

11.3. Special Considerations

11.3.1 Adverse Events of Special Interest

Since topical retinoids are associated with local application site AEs, particularly when beginning treatment, these events will be followed closely during the study and considered AEs of special interest (AESIs).

11.3.2 Pregnancy

All WOCBP who participate in the study should be counseled on the need to practice highly effective birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during IP treatment will be immediately discontinued from study treatment. The investigator must report the pregnancy of any woman who becomes pregnant during or within 30 days after discontinuing treatment as if it were an SAE within 24 hours of learning of the pregnancy, to Premier Research Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. If a partner of a male study subject becomes pregnant, the investigator must report the pregnancy as soon as possible after learning of it to the Premier Research Pharmacovigilance using the Pregnancy Data Collection Form. A separate pregnant partner ICF will be required.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy in a study subject. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Pregnancy Data Collection Form and forwarded to Premier Research Pharmacovigilance. The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly. In such case, an additional form (Serious Adverse Event Report Form) must be filled out by the investigator and provided to Premier Research Pharmacovigilance within 24 hours of knowledge of the pregnancy's serious outcome.

Among the clinical studies, 12 pregnancies were reported: 4 resulted in normal births; 5 resulted in spontaneous abortions (none of which was considered related to CD5789); 1 was electively

aborted, and 2 were lost to follow-up (Investigator's Brochure for CD5789 Cutaneous Formulation).

12. DATA SAFETY MONITORING BOARD

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including LI. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate under a charter that will be finalized prior to the start of the study. The DSMB will meet at least 3 times during the conduct of the study: when the study begins, when 15 adult subjects have enrolled in Cohort A and have completed at least 28 days of treatment, and after 60 subjects have enrolled in the study.

The DSMB will meet after 15 subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data (including PK and ECG results). The safety data will be unblinded to the DSMB. At that time, the DSMB will decide whether Cohort B (adults and subjects aged 12–17) may begin enrolling, or if additional adult safety data are required before allowing subjects aged 12 – 17 to participate in the study. The DSMB will have the authority to recommend to the sponsor that the study be modified, placed on hold, or stopped if serious safety issues are discovered. The DSMB will provide its input to Mayne Pharma LLC. Any protocol changes the DSMB may suggest will be submitted to all applicable regulatory bodies for review and approval.

In case of significant toxicity, the DSMB may choose to review the available safety data and recommend stopping recruitment in a particular dose group.

Stopping rules for individual subjects are in Section 8.4. The DSMB committee members are as follow:

- Univ. Prof. Dr. med. Steffen Emmert, Director at Clinic and Polyclinic for Dermatology & Venereology University Medical Center Rostock
- Jeffrey Louis Sugarman, M.D., Ph.D. Pediatric Dermatologist
- Moise L. Levy, MD, Pediatric Dermatologist
- Gabriele Accetta, Ph.D,. Biostatistician

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. A SAP that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a P value of ≤ 0.05 will be considered statistically significant.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will include the number and percentage of subjects in each category.

The primary analysis period is the first 90 days of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after the database is locked. A second analysis will take place for endpoints assessed from Day 90 through the OLE Period. The baseline for the safety and efficacy parameters will be measured at Visit 1 or Visit 2, per the Schedule of Events for both the Double-blind Period (Table 2-1) and OLE (Table 2-2).

13.1.1 Analysis Populations

The following 5 analysis populations are planned for the Double-blind Period of this study:

- Safety: all subjects who are randomized to treatment and receive at least 1 application of study drug in the Double-blind Period. This population will be the primary population for analyses of safety.
- Intent-to-treat (ITT): all randomized subjects. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study.
- Modified intent-to-treat (mITT): all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period.
- Per-protocol (PP): subjects in the mITT Population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations.
- Pharmacokinetic: all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. This population will be used to summarize all PK endpoints.

The following analysis populations are planned for the OLE of this study:

- OLE Safety: all subjects who complete the 90-day Double-blind Treatment Period and receive at least 1 application of study drug in the OLE.
- OLE ITT: all subjects who complete the 90-day Double-blind Treatment Period and sign the OLE informed consent.
- OLE mITT: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6.
- OLE PP: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study.

Inclusion in the analysis populations will be determined prior to database lock. Deviations related to COVID-19 will also be evaluated in determining PP population eligibility.

If a subject is randomized incorrectly or is administered the incorrect IP, analyses of the ITT and mITT populations will be based on the assigned treatment whereas all other analyses will be based on the actual treatment received.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

For the Double-blind Period, the numbers of subjects randomized, completing Day 90 of the study, and withdrawing early from the Double-blind Period, along with reasons for withdrawal, will be tabulated overall and by randomized treatment group. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated by randomized treatment group. This analysis will be conducted for the ITT population.

For the OLE, the number of subjects entering the OLE, completing the study, and withdrawing early, along with reasons for withdrawal, will be tabulated overall. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated. This analysis will be conducted for the OLE ITT population.

13.1.2.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations promptly. All deviations must be addressed in study source documents, and reported to Premier Research or Mayne Pharma LLC. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

Subjects who taper to once-weekly application or who take a “drug holiday” will not be reported as having deviated from the protocol.

13.1.2.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for the ITT and OLE ITT populations.

Demographic variables will include age, sex, race, ethnicity, height, weight, and BMI. Baseline subject characteristics will include medical history, physical examination findings, and IGA score.

Prior and concomitant medications will be summarized by randomized treatment group, by the number and percentage of subjects taking each medication, and classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of each subject’s dose, and in terms of duration of exposure for each period. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group.

Additionally, the number of subjects who are compliant with investigational product will be presented by treatment group for the Double-blind Period and overall for the OLE.

Subjects who taper to once-weekly application or who take a "drug holiday" will not be reported as having deviated from the protocol.

13.1.4 Efficacy Analysis

The ITT population will be used as the primary population for the primary analysis of efficacy at Day 90. Select efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE using the OLE ITT, OLE mITT, and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE.

Efficacy endpoints will be based on investigator assessment.

13.1.4.1 Efficacy Endpoints

Primary efficacy endpoint: The proportion of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 2-grade change from Baseline at Day 90/EOT in the Double-blind Period on the 5-point IGA scale.

Secondary: The secondary endpoints are as follow:

- The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Day 90:
  - 5-point VIIS scale for scaling
  - Individual score for roughness (Scale: 0–4)
  - Palm/sole Assessment (Scale: 0–4)
  - Quality of life per DLQI and cDLQI
- The difference in proportion of subjects with presence of fissures on palm/soles (presence/absence, number of fissures, and pain associated with fissures [on a 0-3 scale]) at Day 90 between the active trifarotene cream HE1 and vehicle groups

Exploratory: The exploratory endpoints are as follow:

- The difference in mean ectropion scores (ESS of 0–8) between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90
- The difference in quality of life per EQ-5D-5L and EQ-5D-Y scores between the active trifarotene cream HE1 and vehicle groups from Baseline through Day 90

13.1.4.2 Primary Analysis

For the Double-blind Period only, the number and proportion of subjects in each treatment group with successful resolution of LI by Day 90/EOT will be presented. The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the

odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group, 95% CIs for the differences, and P-values for the differences in treatment will also be presented.

Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from baseline will be provided for IGA scores for both periods.

13.1.4.3 Secondary Analyses

Secondary and exploratory efficacy endpoints will be analyzed separately for each period (Double-blind and OLE) using descriptive statistics.

Additionally, for the Double-blind Period only, change from Baseline in continuous secondary endpoints through Day 90 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate.

For subjects who report having fissures, descriptive summaries of the number of fissures and pain related to fissures will also be presented by treatment group and body area for each period.

The DLQI scores will also be analyzed using descriptive statistics through Day 90.

The proportion of subjects with at least a 50% reduction in IGA score from Baseline will be analyzed using the same logistic regression analysis described in Section 13.1.4.2.

13.1.4.4 Exploratory Analyses

Descriptive summaries and the changes from baseline will be provided for ectropion scores and EQ-5D-5L scores by visit for each period. No formal inferential analyses will be conducted for exploratory endpoints.

13.1.4.5 Corroborative, Sensitivity, and Other Analyses

To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using multiple imputation (MI) for the Double-blind Period only. Multiple-imputations will be used to replace missing IGA outcomes using multiple draws from the posterior predictive distribution estimated from the treatment groups. IGA scores will be imputed and then categorized as treatment success according to Section 13.1.4.1. Imputation will not be performed for the OLE. Full details will be specified in the SAP.

Thorough assessment on the extent of missing data and procedural adjustments due to COVID-19 as it pertains to the primary and secondary efficacy endpoints will be conducted ahead of database lock, and additional sensitivity analyses may be performed. Full details will be documented in the SAP.

The proportion of subjects who experience a 2-grade change from baseline to Day 90 in individual score for roughness and palm/sole assessment will also be explored using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in

proportions between the active trifarotene cream HEI and vehicle cream group and the 95% CIs for the differences will be presented.

For analyses involving study site, if the number of subjects per site is small, sites may be pooled for safety and efficacy analysis or omitted from statistical models as the anticipated number of subjects per site is small, treatment is self-administered, and the sites are using standardized procedures for all assessments. If the distribution of enrollments at sites is such that one or few are enrolling a majority of subjects, a subgroup analysis by site may be performed. The final determination will be made prior to database lock.

Details of these analyses will be further detailed in the SAP.

13.1.5 Clinical Pharmacology Analyses

13.1.5.1 Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics. Descriptive statistics reported will include the arithmetic mean, SD, CV%, geometric mean, minimum, maximum, and median. Only the range and the median will be reported for T_{max}, as this is a categorical parameter. The PK parameters will also be summarized by treatment using descriptive statistics.

Individual plasma concentration plots and mean data graphs will be produced using both linear and semi-logarithmic scales. Mean data graphs will show plasma concentration profiles by treatment group.

Pharmacokinetic plasma parameter estimates and summaries will be completed for the subjects in the PK population. Testing of PK parameters will be outlined in the SAP.

13.1.6 Safety and Tolerability Analyses

Safety analyses through Day 90 of the Double-blind Period will be conducted using data from the Safety Population and safety analyses in the OLE will be conducted using the OLE Safety Population (as defined in Section 13.1.1). Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, and physical examination results. No formal inferential analyses will be conducted for safety variables in either period.

13.1.6.1 Local Tolerability

During all clinic visits, the investigator will assess local tolerability (stinging/burning, pruritus, or erythema on 0-3 scales [none, mild, moderate, severe]) for each treated body area (chest/abdomen, back, arms, legs, and face/neck). Descriptive summaries will be presented by period, treatment group, and visit.

13.1.6.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1 or higher.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first, or
- AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first.

The number and percentage of subjects with AEs will be displayed by each treatment group in the Double-blind Period and overall in the OLE by system organ class and preferred term. Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.6.3 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each treatment group at each time point in each period.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory parameter by treatment group and by study visit in each period.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.1.6.4 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for SBP, DBP, and pulse for each period.

The number of subjects with vital signs values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each parameter by period, by treatment group and by study visit. Pre and post-treatment values may also be presented with an analysis of mean changes from baseline.

13.1.6.5 Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point in each period. Abnormal results will be grouped as clinically significant and not clinically significant.

A comparison of QT results will be presented. Summary statistics will be displayed by period, by treatment group, and by visit for QT and the QT interval corrected for heart rate (QTc) calculated using Fridericia's QT correction methods.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTcF interval (Fredericia's correction methods), and HR for each treatment group at each time point in each period.

13.1.6.6 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group in each period.

13.1.7 Interim Analysis

No interim analyses are planned.

13.2. Sample Size Determination

Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively. This study is not powered to detect a difference between the 2 active arms.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Mayne Pharma LLC agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with ICH GCP, and the applicable United States (US) Code of Federal Regulations (CFR). The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IP(s), and their specific duties within the context of the study. Investigators are responsible for providing Mayne Pharma LLC with

documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Premier Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Premier Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Premier Research.

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory/GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening Visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4. Study Documents

All documentation and material provided by Mayne Pharma LLC for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Consent and assent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The informed consent and assent forms are submitted with this protocol.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent and assent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent and assent forms and ask questions before signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate. The participant will sign the informed consent or assent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent and assent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory/Good Clinical Practice Documents

The regulatory/GCP documents are listed below.

- Signed original protocol (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and subinvestigators
- Name and address of the laboratories

- List of laboratory reference ranges, and if available, a quality certificate
- Form Signature Log/Delegation of Study-related Duties
- Approved ICF and subject materials
- FDA1572 and financial disclosure forms, as applicable (US sites)
- Any other relevant GCP documents

The regulatory/GCP documents must be received from the investigator and reviewed and approved by Mayne Pharma LLC or its designee before the study site can initiate the study and before Mayne Pharma LLC will authorize shipment of IP to the study site. Copies of the investigator's regulatory/GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the trifarotene (CD5789) Cream IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and IP accountability records should also be retained as part of the investigator's regulatory/GCP documents. It is the investigator's responsibility to ensure that copies of all required regulatory/GCP documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.5. Data Quality Control

Mayne Pharma LLC and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

Mayne Pharma LLC and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Mayne Pharma LLC personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures
- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF will be provided to the sites. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Mayne Pharma LLC or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan (CMP).

14.5.2 Data Management

Mayne Pharma LLC or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data management plan (DMP) will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries will be provided to the sites.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Mayne Pharma LLC or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits

- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or clinical study report [CSR])

Mayne Pharma LLC or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Mayne Pharma LLC immediately.

14.6. Study Termination

The study may be terminated at Mayne Pharma LLC's discretion at any time and for any reason.

The DSMB may recommend discontinuation of the study if they find evidence of unacceptable risk to subjects.

14.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, Mayne Pharma LLC or designee will notify the IECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

14.6.2 Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by Mayne Pharma LLC, IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Mayne Pharma LLC or its designee will notify the IECs and regulatory authorities about the premature termination as required according to national laws and regulations. Mayne Pharma LLC or its designee must clearly explain the reasons for premature termination.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the IND or IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is terminated prematurely, all investigators have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Follow-up Visit.

The study might resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or FDA.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. Mayne Pharma LLC may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1 Record Retention

For sites in the US, the investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until 1 of the following occurs:

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

Outside of the US, after completing the study, Mayne Pharma LLC will receive the original eCRFs or at least a legible copy and retain the documents for at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be

retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

14.7.2 Sample Retention

Blood samples will be used for purposes related to this study only, and will not be stored for future research. The samples will be stored until they are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

Data collected for this study will be analyzed and stored at Premier Research.

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Mayne Pharma LLC. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9. Use of Information and Publication

All information concerning trifarotene (CD5789) cream HE1, Mayne Pharma LLC's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Mayne Pharma LLC or its designee to the investigator, and not previously published, is considered confidential and remains the sole property of Mayne Pharma LLC. Case report forms also remain the property of Mayne Pharma LLC. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by Mayne Pharma LLC in connection with the continued development of trifarotene (CD5789) cream HE1 and thus, may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Mayne Pharma LLC. Publication or other public presentation of trifarotene (CD5789) cream HE1 data resulting from this study requires prior review and written approval of Mayne Pharma LLC. Abstracts, manuscripts, and presentation materials should be provided to Mayne Pharma LLC for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until Mayne Pharma LLC has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be

registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

15. FINAL CLINICAL STUDY REPORT

Mayne Pharma LLC will retain ownership of the data.

The final CSR will be written within 6 months of completion of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

16.2. Subject Information and Informed Consent and/or Assent

A properly constituted, valid IRB or IEC must review and approve the protocol, the investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent and/or assent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed assent or consent prior to enrollment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent and/or assent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Mayne Pharma LLC, and/or the

sponsor's designee. Collection of informed consent and/or assent has to be documented in the eCRF.

Furthermore, the subject will be informed that if he or she wishes to drop out or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

16.3. Approval by Institutional Review Board and Independent Ethics Committee

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's or the sponsor's representative before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must follow local country requirements.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by Mayne Pharma LLC before implementation.

16.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

17. REFERENCES

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3. Vahlquist A, Gånemo A, Virtanen M. Congenital ichthyosis: an overview of current and emerging therapies. *Acta Derm Venereol.* 2008;88(1):4–14.
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12. Chiaretti A, Wismayer DS, Tortorolo L, Piastra M, Polidori G. Salicylate intoxication using a skin ointment. *Acta Paediatr*. 1997;86(3):330-331.
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18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER: 18-ICH-001

PROTOCOL TITLE: A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 90-Day, Safety, Efficacy, and Systemic Exposure Study followed by a 90-Day Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale

AMENDMENT 2 DATE: 28-Oct-2020

The undersigned acknowledges possession of and has read the product information (e.g., investigator's brochure) on the IP and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected subjects in his/her care, according to the study protocol.

He or she agrees to use the study material, including IP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Mayne Pharma LLC.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Mayne Pharma LLC within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IP.

He or she agrees to comply with Mayne Pharma LLC and regulatory requirements for the monitoring and auditing of this study. In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

APPENDICES

A. Regulations and Good Clinical Practice Guidelines

B. Procedural Adjustments Due to COVID-19

A. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives (and applicable regulations/guidances):

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents>

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

B. Procedural Adjustments Due to COVID-19

The coronavirus (COVID-19) global pandemic has impacted the free movement of the world's population, which has been restricted to control the spread of the disease. It is recommended that all sites and subjects comply with the applicable local and federal guidelines regarding the necessary and proper precautions regarding COVID-19.

Trifarotene cream HE1 does not increase the risk for contracting COVID-19.

Although it is preferable to conduct all necessary study assessments in person (on -site visits), this may not be possible as a result of COVID-19 -related travel restrictions site closures, or subject confinement. If the subject becomes infected with COVID-19, the investigator or the treating physician will decide on continuation of the study treatment; note that topical trifarotene does not modify immunity.

The skin of individuals with LI is thick, scaly, and often dry, tight, and inelastic. This rigidity may produce major discomfort through formation of painful cracks in the skin and open areas. Extreme thickening of the skin on the soles of the feet can make walking difficult for many patients, and cracks and fissures on the fingers can make even simple tasks difficult or painful. Tight skin can interfere with joint mobility, and over time, lead to decreased joint mobility. Some individuals may be unable to close their eyes completely (ectropion) because of the tightness of the skin around the eyes and eyelids and may seem to "sleep with their eyes open." In addition, the general aspect of this chronic and difficult to manage skin disease often causes depression. For these reasons, as well as the lack of treatment options for individuals with LI, Mayne Pharma thinks it is important for this patient population to continue having access to the treatment offered in this study.

The best way to ensure the reliability of the data collected is to follow the Study Protocol. However, the subjects' safety and wellbeing is a top priority. Therefore, in extraordinary situations when it is inadvisable or not possible to conduct an onsite study visit, please follow these procedures.

❑ **Subject visits:**

Visits 3 to 6 of the Double-blind Period, Visits 7 to 11 of the OLE Period, and unscheduled visits may be conducted remotely (i.e., via telephone or video call). Screening and Baseline Visits must be performed onsite only and must be postponed or scheduled for when onsite visits can be safely conducted. The schedule of telephone visits will continue as indicated in the study protocol (Table 2-1 and Table 2-2); however, onsite visits will be postponed or rescheduled as possible.

When it is not possible to postpone or reschedule the onsite visit, and to ensure the safety of the subjects and to not jeopardize the study procedures and the scientific value of the trial, onsite visits will be changed into telephone visits. As soon as the COVID-19 situation that triggered the use of these procedural adjustments is resolved, the schedule of onsite visits will resume. Information collected during the telephone visits will focus on safety data and primary objective endpoints. The following information is expected to be collected by the PI/study staff during the telephone visits, as applicable per protocol:

- Ask/remind the subject about any required study procedure considered necessary and according to the protocol. For example:

  - Ask the subject about study drug application
  - Remind the subject to complete the subject diary
  - Advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days
- Record concomitant medications and concomitant therapies
- Record Adverse Events and information reported in the subject diary
- Record the subject's general health status
- Assess local tolerance at the application sites
- For efficacy assessments, use videoconference for precise scoring; if this is not possible, ask subject if status is the better, worse, or unchanged for the following assessments and enter the outcome for reference in the source data:
  - Investigator's Global Assessment (IGA)
  - Visual Index for Ichthyosis Severity (VIIS)
  - Roughness
  - Palm/sole
  - Palm/sole fissuring
  - Ectropion
- Record urine pregnancy test result for female subjects
- Evaluate treatment compliance, including frequency of application and check if there is cream left in the tubes after application and approximately how much in conjunction with the subject's diary
- Adjust the treatment if necessary, as per study protocol, according to application site tolerance and treatment compliance

Remote visits are not possible in the following instances:

- Baseline visits will be canceled if the subject is unable to go to the site. If this occurs, rescreening may be necessary when the COVID-19 outbreak is resolved.
- End-of-Treatment visits are recommended to occur onsite. Therefore, the telephone visit will be completed, followed by an onsite visit when the COVID-19 outbreak is resolved.

❑ **Pregnancy Tests**

Retinoids are potentially teratogenic and, therefore, monthly pregnancy tests for women of childbearing potential (WOCBP) are considered critical for subject safety. Consequently, urine pregnancy tests, along with the instructions on how to use them, will be sent to the subject's home. The study staff will instruct the subjects how to properly perform the test during the telephone visits and will document it and the result.

❑ **Supply of Study Medication**

For all randomized subjects who have already attended the baseline visit (Day 1) and, have had study staff apply the first administration of the study drug in the clinic and instructed the subject,

should continue their treatments to ensure the reliability of the study data and the scientific value of the trial. Therefore, if the subject is not able to travel to the site, the site will ship the study drug and to the subject's home using their preferred local courier service. Patient diaries may be sent to subjects electronically or via postal service. Completed diaries may be returned to the site in the same manner.

Investigators/site staff will properly record that the subject has been told their study medication will be sent to their home, and when the study medication was received. Subjects should retain any unused IP and return them to the study site at the next onsite visit, when the study staff will weigh the kits (tubes and boxes, but not leaflets).

- **Quality of life per Dermatology Life Quality Index (DLQI) and EQ-5D Quality of Life Questionnaire**

Quality of Life questionnaires should be completed on the day of the remote visit and prior to applying treatment (if the remote visit falls on a treatment day). Questionnaires may be sent to subjects electronically or via postal service, and completed questionnaires may be returned to the site in the same manner. If subjects are unable to send completed questionnaires to the site, investigators should ask and record the subject's responses during the remote visit.

However, questions relative to social interaction might not be relevant due to social distancing and/or quarantining. This will be captured in the questionnaires and can be differentiated in the analysis.

- **Monitoring visits:**

If onsite monitoring visits are not possible as a consequence of COVID-19 outbreak, remote visits (via telephone) will be arranged in agreement with the study sites to assist the study progression and to ensure study compliance, without reducing the level of monitoring.

- **Participant Information**

Participating subjects must be promptly informed about changes in the study conduct during COVID-19 outbreak. Information about the changes should first be communicated to subjects via a telephone conversation.

In addition, a Subject Information Sheet has been created to inform subjects about how the above-mentioned changes might impact their usual participation in the study. The investigators/study staff will send this information sheet to the subject by the appropriate means (for example, via email or via courier). Investigators/study staff will confirm and document in the medical history the date the patient was informed via telephone and the date the Subject Information Sheet was mailed to and received by the subjects.

❑ **Informed consent and/or assent process recommendations**

Where country regulation requires that the COVID-19 Information Sheet is signed by the subjects to express their consent to the changes in the study procedures due to COVID-19 or a subject is completing the double-blind part of the study and needs to consent to continue in the open label extension part, the process will be as follows:

1) First option is to collect face-to-face written consent with the investigator according to ICH E6 (R2) and local regulation.
2) When face-to-face written consent is not possible trial participants can be contacted via phone or video call to obtain remote consents as follows:
    a. Informed consent document/assent, if applicable, is emailed, faxed, or sent via courier or regular mail by site staff to subject prior to remote visit.
        - If document is emailed, subject should print document prior to visit.
    b. Subject will be contacted via phone or video call* by the investigator/designee. Informed consent/assent discussion with the subject will be facilitated by the Investigator or staff delegated to perform this task
        - Investigator/designee will document details of the remote informed consent process in the trial participant's medical records.
    c. Subject will sign and date informed consent/assent while on phone or video call with Investigator/designee
        - Investigator/designee will document the time and date that they witness the signing of the informed consent/assent via phone or video call in the trial participant's medical records.
    d. Investigator/designee will sign and date copy of the Informed consent/assent documenting that they witnessed the signature of the subject via phone or video call
    e. Subject will send signed and dated informed consent by email or courier back to investigational site to be included in the subject file.
        - If sent by email, subject should save the original copy and bring it to his/her next onsite visit.
    f. Investigator/designee will attach the subject signed Informed consent/assent to the copy signed and dated by Investigator/designee upon receipt.
    g. When subject returns to the site, consent will occur face-to-face with site staff according to ICH E6 (R2) and local requirements.

*Video call will be used only if allowed per country regulation. If you have doubts on whether video call can be used in your country, please contact your CRA.

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FILE NOTE

Note: Retain a word version of this file note to permit later updates/additions. All updates/additions must be resigned. Date each entry for updates.

TYPE	Protocol
PROTOCOL	Mayne 18-ICH-001 Amendment 2.0
EFFECTIVE	03-Nov-2020 ☒ Tick here if Permanent
TITLE	Date change in protocol amendment 2.0
FUNCTIONS AFFECTED	Medical Writing/Clinical/SSU
PURPOSE AND DETAILS Provide all necessary information, being clear and concise. For file notes resulting from audits, DO NOT refer to the audit, state only the facts. File notes must not contain identifying information e.g., patient names.	Date in footer on p. 2 was incorrect (27-Oct-2020) and was updated after signature to 28-Oct-2020.
ACTIONS /IMPACTS **Provide any corrective and preventative action (CAPA) plan, if applicable.**	Summarise any actions or impacts on general or study specific activities as a result of the reason for this file note. This note to file records the change of the protocol amendment date for p 2 to make consistent throughout the document. No further action is required.

Note: Approval is ALWAYS required for file notes written on behalf of an Investigator.

For all other file notes, if in doubt, check with your Supervisor/Department Head/Project Manager whether approval is required.

AUTHOR:	DocuSigned by: Kristen Drake Signer Name: Kristen Drake Signing Reason: I approve this document Signing Time: 03-Nov-2020 | 12:20:32 EST 52541A3986904639919159 10E145BAE9		03-Nov-2020 | 12:20:41 EST
	Kristen T. Drake Dir, Medical Writing		*Date*
APPROVER:	DocuSigned by: Laura Tran-Viet Signer Name: Laura Tran-Viet Signing Reason: I approve this document Signing Time: 03-Nov-2020 | 12:22:57 EST B32E89A70DFF45F1A759F2A906462BC8		03-Nov-2020 | 12:23:01 EST
	Laura Tran-Viet Project Manager		*Date*

PROTOCOL/CLINICAL INVESTIGATION PLAN AMENDMENT

PRODUCT NAME/NUMBER:	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER:	18-ICH-001
IND NUMBER:	140538
NCT NUMBER:	NCT03738800
EUDRACT NUMBER:	2018-003272-12
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
PROTOCOL DATE:	Original: 28-Nov-2018
AMENDMENT 1 DATE:	Final v2.0, 21-Oct-2019
AMENDMENT 2 DATE:	Final v3.0 for Ukraine, 21-Nov-2019
COORDINATING/PRINCIPAL INVESTIGATOR:	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine, PO Box 208059 333 Cedar Street New Haven, CT 06520, USA +1 203 789 1249
SPONSORED BY:	Mayne Pharma LLC 1240 Sugg Parkway Greenville, NC 27834, USA +1 984 242 1400
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive, Suite 150 Durham, NC 27709, USA +1 919 627 9100

This study will be performed in compliance with ICH Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the institutional review board or independent ethics committee, or as required by law. Persons to whom this information

is disclosed should be informed that it is confidential and may not be further disclosed without the express permission of Mayne Pharma LLC.

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: 18-ICH-001

PROTOCOL TITLE: A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale

I, the undersigned, have read this protocol and confirm that to the best of my knowledge, it accurately describes the planned conduct of the study.

SIGNATURE	**DATE:**
	27 Nov 2019
Ilana Stancovski, PhD Chief Scientific Officer Mayne Pharma LLC	
DocuSigned by: Phoevos Hughes Signer Name: Phoevos Hughes Signing Reason: I approve this document Signing Time: 02-Dec-2019 | 07:35:12 PST 2D1DC1CA65A848718371307AF875E4CE	02-Dec-2019 | 07:35:16 PST
Phoevos Hughes, JD Associate Director, Clinical Operations Mayne Pharma LLC	
DocuSigned by: Marlis Sarkany Signer Name: Marlis Sarkany Signing Reason: I have reviewed this document Signing Time: 02-Dec-2019 | 09:55:35 EST 16E1C8AEDC854CDC86688C1FD466E26F	02-Dec-2019 | 09:55:42 EST
Marlis Sarkany, MD Senior Medical Director Premier Research	
DocuSigned by: Adrienne Kuxhausen Signer Name: Adrienne Kuxhausen Signing Reason: I approve this document Signing Time: 02-Dec-2019 | 10:50:53 EST 6E6B87C6B98740819F26B8D5A7D662CF	02-Dec-2019 | 10:50:55 EST
Adrienne Kuxhausen, MS Senior Biostatistician Premier Research	

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER	18-ICH-001
EUDRACT NUMBER	2018-003272-12
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 12-Week, Safety, and Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
INDICATION	Lamellar ichthyosis
OBJECTIVES	Primary: To compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in subjects with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 12 weeks of treatment. Secondary: • To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% body surface area (BSA) twice weekly. • To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.
STUDY DESIGN	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Investigator's Global Assessment [IGA] where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe). Subjects in Cohort A and Cohort B will be randomized in a double-blind fashion to 1 of 2 doses of trifarotene cream HE1 or vehicle and treated twice weekly for 12 weeks. Subjects who complete the randomized, Double-blind Period of the study will be eligible to enter a 12-week, Open-label Extension (OLE) in which additional PK, safety, and efficacy data will be collected. Approximately 15 subjects will be randomized into the first cohort of subjects (Cohort A) in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks. After the initial 15 subjects complete at least 28 days of treatment, an independent data safety monitoring board (DSMB) will review aggregate safety and tolerability data (including PK and electrocardiogram [ECG] data). If no safety issues are identified, an additional group of approximately 105 subjects will be allowed to enroll in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks in the same manner as subjects in Cohort A. All subjects (Cohort A and Cohort B) who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for up to 12 weeks. Upon signing informed consent and entering the Screening Period, subjects may begin washout, during which they will stop using physical and medical treatments for LI,

including balneotherapy and the following prohibited medications, as applicable. Washout may be up to 3 months, as necessary.

a. Topical treatments

Medication	Washout
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	2 weeks

b. Systemic treatments

Medication	Washout
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines (except Vitamin D analogues taken at stable dose since at least 1 month)	8 weeks
QT prolonging drugs	5 half lives
Enzymatic inductors (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (not all inclusive: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives
Monoclonal antibody treatment (e.g., anti-IL17)	5 half lives

During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower, but not bathe or swim during the Screening Period.

After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.

Study drug will be packaged in 50-g tubes from which up to 36 g of investigational product (IP) may be dispensed per application, i.e., the maximum dose per application. Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied. If the product will be applied at home by someone other than the study subject, it is recommended that this person assist with application at the first visit to learn how the IP is applied.

Thereafter, each subject will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of product in a tube. Subjects will record the date and time of study treatment administration in the subject diary.

	Local tolerability may differ in subjects with LI compared to healthy subjects, as their skin is drier and may be more sensitive. Local tolerability will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45 in the Double-blind Period; at Day 97 and 134 in the OLE) to assess safety; an unscheduled clinic visit may be performed, if necessary. If the treatment causes application site reactions, the frequency of application will be reduced or interrupted only on the area of concern, as indicated herein. During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for stinging/burning, pruritus, erythema) for each body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed: - If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas. - If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas. Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and adverse events (AEs). Any changes in dosing must be documented in the subject diary and the electronic case report form. All subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]) and any AEs, including application site reactions and concomitant medications used. Subjects will also be advised on permitted emollient(s) use on nontreatment days during the study; use of emollient(s) and/or sunscreen(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. At all sites with photographic capability, photographs will be taken as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional photographic informed consent form (ICF). Samples for pharmacokinetic (PK) analysis will be drawn from all subjects at Baseline and at each clinic visit. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained on the skin after the last application. Subjects should not apply IP on visit days until after the visit. In addition, a PK substudy will be conducted on Days 1 and 30 at sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 30 subjects. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for these subjects at each of the other clinic visits. For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30. Subjects who complete the Double-blind Treatment Period will have the option to continue into the OLE to assess safety for an additional 12-weeks with trifarotene cream HE1 200 µg/g twice weekly, on up to 90% of BSA, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. During the OLE, subjects will return to the site at Weeks 14, 16, 20, 24, and 26 for safety,

	tolerability, and efficacy assessments. Blood samples will be drawn for clinical laboratory safety tests and PK at Weeks 16 and 24. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 97 and Day 134) to assess safety; an unscheduled clinic visit may be performed, if necessary.
PLANNED NUMBER OF SUBJECTS	Approximately 120 total subjects; 15 subjects in Cohort A and 105 subjects in Cohort B.
STUDY ENTRY CRITERIA	Inclusion criteria: 1. Subject is ≥18 years old. 2. Subject has known diagnosis of LI. 3. Subject has moderate to severe (IGA 3-4) LI on the IGA of LI severity. 4. Subject has signed an ICF at Screening before any investigational procedures. 5. Subject who is participating in photography has signed a photography ICF. 6. Subject who is participating in the optional PK substudy has signed a PK ICF. 7. Subject is not of childbearing potential, i.e., a female who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason, hysterectomy or bilateral oophorectomy), OR Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception: • bilateral tubal ligation • combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline OR Agrees to abstain from heterosexual intercourse during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. AND Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application. 8. Women of childbearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine). 9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent. 10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

	Exclusion criteria: 1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization, including syndromic ichthyoses. 2. Subject has current moderate or severe stinging/burning at Screening. 3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments. 4. Subject with a known lipid disorder (hypertriglyceridemia >200 mg/dL, hypercholesterolemia >250 mg/dL) unless well controlled by stable doses of lipid-lowering agents for at least 6 months. 5. Subject was previously treated with trifarotene/CD5789 in an acne or ichthyosis study. 6. Subject has any other significant concomitant disease, or poorly controlled medical condition other than LI that in the investigator's opinion may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis). 8. Subject is being treated for major depression disorder and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts. 9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening. 10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory b. Total bilirubin >1.1 mg/dL or, in case of Gilbert's syndrome, total bilirubin >3 mg/dL c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women d. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L 11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 12. Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment. 13. Subject has a history of long QT syndrome or clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, QTcF interval >450 ms, PR interval is not between 120 and 220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed. 14. Subject has a known allergy or sensitivity to any of the components of the investigational products. 15. Subject has been exposed to excessive ultraviolet (UV) radiations on the treated zones within 1 month before Baseline visit or is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.). 16. Subject is inherently sensitive to sunlight. 17. Subject is unable or unwilling to stop use of topical or systemic retinoids.

	18. Subject is presumed to be abusing drugs or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms. 19. Subject is participating in another interventional clinical trial. 20. Subject is institutionalized. 21. Subject is in any way related to the sponsor, investigator, or site personnel.
INVESTIGATIONAL PRODUCT	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Extension dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 200 µg/g applied topically twice weekly on up to 90% BSA
REFERENCE PRODUCT	Name: Vehicle cream Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) applied topically twice weekly on up to 90% BSA
TREATMENT REGIMENS	Topical application twice weekly to all affected skin except the scalp, axillae, and inguinal area.
COORDINATING/ PRINCIPAL INVESTIGATOR	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine New Haven, CT 06520, USA
PLANNED STUDY SITES	Approximately 40 sites across North America, Europe, Israel, and Australia

CRITERIA FOR EVALUATION	Primary efficacy endpoint: The proportion of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear on treated areas and at least a 2-grade change from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA full body scale. Secondary endpoints: – The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Week 12: – 5-point Visual Index for Ichthyosis Severity (VIIS) for scaling from Baseline through Week 12 (overall 16 points for scaling, i.e., 0-4 points for 4 body areas: chest/abdomen, back, arms, and legs) – Individual score for roughness (Scale: 0–4) overall – Palm/sole Assessment (Scale: 0–4) • Quality of life per Dermatology Life Quality Index (DLQI) – The difference in proportion of subjects with presence of fissures on palms/soles (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) at Week 12 between the active trifarotene cream HE1 and vehicle groups Exploratory endpoints: – The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12 – The difference in quality of life per EQ-5D-5L score between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12 Safety endpoints: – Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs – Local tolerability (Scale: 0-3 [none, mild, moderate, severe], determined by the investigator) for each body area (chest/abdomen, back, legs, arms, and face/neck). Pharmacokinetic endpoints: Plasma concentrations of CD5789 and its major metabolites will be measured.
STATISTICAL METHODS	Analysis Populations: The following are planned for the Double-blind Period of the study: The Safety population will be the primary population for analyses of safety and tolerability and will comprise all subjects who are randomized to treatment and receive at least 1 application of study drug. The intent-to-treat (ITT) population will comprise all randomized subjects. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The modified intent-to-treat (mITT) population comprises all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The per protocol (PP) population will be defined prior to database lock and will comprise subjects in the mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations.

	The PK population includes all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. The PK population will be used to summarize all PK endpoints. The following populations are planned for the OLE of this study: The OLE Safety population: all subjects who complete the 12-week Double-blind Treatment Period and receive at least 1 application of study drug in the OLE. OLE ITT population: all subjects who complete the 12-week Double-blind Period and who sign the OLE informed consent. The OLE mITT population: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6. The OLE PP population: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study. Subject Characteristics and Disposition: Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and baseline characteristics for all enrolled subjects. Medical history, physical examination findings, and vital sign measurements for all randomized subjects will be presented in listings. Efficacy Analyses: The number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT in the Double-blind Period will be presented. The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream groups, 95% CIs for the differences, and P-values for the differences in treatment will also be presented. The IGA scores as well as secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Week 24. Change from Baseline through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from Baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and Baseline score value as a covariate. Frequencies of results and 95% confidence intervals will also be reported, and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test. For subjects who report having fissures, the number of fissures and pain related to fissures will also be presented on a scale of 0-3 (none, mild, moderate, severe). Clinical Pharmacology Analyses: Noncompartmental PK analysis will be performed for the PK subset of subjects, as data permit. Plasma concentrations of CD5789 and its major metabolites will be measured and will be listed by subject. Safety Analyses: Safety and tolerability will be assessed based on the incidence of reported TEAEs, and SAEs, including relationship to study drug and severity, as well as physical examination findings, vital sign measurements (supine systolic blood pressure [SBP] and diastolic blood pressure [DBP] and pulse), clinical laboratory results (hematology, including serum aminotransferases and serum lipids, coagulation, clinical chemistry, and urinalysis) and 12-lead ECGs. Descriptive statistics for observed values and change from Baseline will be calculated at each visit within each study period and by treatment group within cohort.

SAMPLE SIZE DETERMINATION	The first cohort of 15 subjects is a reasonable sample size to assess safety and tolerability before enrolling additional subjects in Cohort B. Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively. This study is not powered to detect a difference between the 2 active arms.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study will be as follows: 1. Screening: Up to 35 days (after signing informed consent, if necessary, washout may be up to 3 months, and subjects should return to the site after washout to complete the study eligibility requirements). 2. Double-blind study drug application: Twice weekly for up to 12 weeks. 3. Optional Open-label Extension: Twice weekly for up to 12 weeks. 4. Follow-up: 14 days after last study drug application. The maximum study duration for each subject is approximately 229 days (33 weeks). The maximum treatment duration for each subject is 24 weeks.

2.2. Schedule of Events

Table 2-1: Schedule of Events for Double-blind Period

	Screening (-35 days to -1 day) Washout up to 3 months[a]	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[b,c] ± 7 days (ET)
Visit	**1**	**2**		**3**	**4**		**5**	**6**
Week		**1**		**2**	**4**		**8**	**12**
Written informed consent	X							X[a]
Assign screening number	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical history	X							
Physical examination	X	X[d]						X[c]
Vital signs (blood pressure and pulse)	X	X		X	X		X	X
Height, weight, and BMI	X							X
IGA assessment[e]	X	X		X	X		X	X
VIIS[f] assessment	X	X		X	X		X	X
Roughness assessment[g]	X	X		X	X		X	X
Palm/sole assessment	X	X		X	X		X	X
Palm/sole fissuring assessment[h]	X	X		X	X		X	X
Ectropion score	X	X		X	X		X	X
Photographs[i]		X			X			X
Quality of life per Dermatology Life Quality Index (DLQI)		X		X	X		X	X

	Screening (-35 days to -1 day) Washout up to 3 months[a]	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[b,c] ± 7 days (ET)
Visit	**1**	**2**		**3**	**4**		**5**	**6**
Week		**1**		**2**	**4**		**8**	**12**
EQ-5D Quality of Life Questionnaire		X		X	X		X	X
12-lead ECG[j]	X	X			X			X
Clinical laboratory tests (hematology, chemistry, urinalysis)[k]	X	X			X			X
Serology (hepatitis B surface antigen, hepatitis C)	X							
Pregnancy test for female subjects (serum at Screening; urine subsequently)	X	X			X		X	X
Randomization via IWRS		X						
PK blood sample collection[l]		X		X	X		X	X
Initial study drug application by clinic staff and measurement[m]		X						
Application instructions, advice on emollient and sunscreen use		X	X	X	X	X		
Dispense study drug and diaries[n]		X[n]		X	X		X	
Concomitant medications	X	X	X	X	X	X	X	X
Tolerability assessment		X		X	X		X	X
Adverse events (and review diaries)		X	X	X	X	X	X	X
Collect all used/unused study drug[o]				X	X		X	X
Provide information about OLE option					X	X	X	

Abbreviations: BMI = body mass index; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears,

nose, throat; ICF = informed consent form; IGA = Investigator's Global Assessment; IWRS = interactive web response system; OLE = open-label extension; PK = pharmacokinetic; WOCBP = women of childbearing potential; VIIS = Visual Index for Ichthyosis Severity

a. Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods, as applicable. Washout may be up to 3 months, as necessary. During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower, but not bathe or swim during the Screening Period. After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.
b. Day 90 procedures should be conducted for subjects who terminate the study early. If a subject discontinues IP, but continues to attend clinic visits, Day 90 will occur as scheduled. Day 90/Week 12 will be the first visit of the OLE for subjects who choose to continue (subjects will have up to 7 days to decide to sign the ICF and begin the OLE). Subjects who decide to continue into the OLE will have the following additional procedures: 1) sign informed consent; 2) will be weighed; 3) will be instructed on study drug application; 4) will be given new diaries, and 5) will be provided with study drug.
c. A Follow-up telephone call will be made within 14 days after Day 90 to subjects who choose not to continue into the OLE.
d. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
e. IGA: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe.
f. VIIS scale for each body area: chest/abdomen, back, legs, and arms, for a possible overall score = 16.
g. Roughness (0-4 scale);
h. Palm/sole fissuring assessment: present/absent/number/pain (0-3 scale).
i. Photography will be performed at sites with the capability for subjects who sign a photographic ICF. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check.
j. ECG to be conducted at Screening, Baseline, Day 30, and Day 90 for all subjects. Subjects in the PK substudy will also have postdose ECGs at each serial blood draw on Day 1 and Day 30.
k. Subjects must be fasting (i.e., at least 8 hours)
l. Samples for PK will be drawn from all subjects at Baseline and at each clinic visit. At selected sites among subjects who consent to participate in the PK substudy, samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1. On Day 30, IP will be applied in the clinic for PK substudy subjects, and PK samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose. Trough levels will be drawn when the subjects are in the clinic for other study visits (i.e., Day 14, Day 60, and Day 90). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.
m. Study staff will apply initial dose of study drug in the clinic after Baseline measurements, and the amount of study drug used will be measured (i.e., 36-g tube will be measured before and after application to determine amount used) to determine fixed dose.
n. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug tubes before dispensing; subjects must record days/times of study drug application in the diaries and any areas of skin not treated, e.g., due to local reactions). Dispense enough additional study drug until next visit (except at Day 90, unless subject consents to continue into OLE).
o. Confirm study drug compliance by measuring tube weight and reviewing diary.

Table 2-2: Schedule of Events for Open-label Extension

	Open-label Treatment Period						**Follow-up**
	Telephone Visit (Day 97)[a]	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7**	**8**		**9**	**10**	**11**
Week		**14**	**16**		**20**	**24**	**26**
Informed consent[a]							
Physical examination[b]						X	X
Vital signs (blood pressure and pulse)			X	X		X	X
Weight	X						
Record IGA[c]		X	X		X	X	X
VIIS[d] assessment		X	X		X	X	X
Roughness assessment[e]		X	X		X	X	X
Palm/sole assessment		X	X		X	X	X
Palm/sole fissuring assessment		X	X		X	X	X
Ectropion score			X	X		X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)[f]			X			X	
Pregnancy test for female subjects (urine)			X		X	X	X
ECG			X			X	
PK blood sample collection[g]			X			X	
Application instructions, advice on emollient and sunscreen use[h]	X	X	X	X			

	Open-label Treatment Period						Follow-up
	Telephone Visit (Day 97)[a]	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7**	**8**		**9**	**10**	**11**
Week		**14**	**16**		**20**	**24**	**26**
Dispense study drug and diaries[i]		X	X		X		
Concomitant medications	X	X	X	X	X	X	X
Tolerability assessment		X	X		X	X	
Adverse events (and review diaries)	X	X	X	X	X	X	X
Collect all used/unused study drug[j]		X	X		X	X	

Abbreviations: ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears, nose, throat; ICF = informed consent form; IGA = Investigator's Global Assessment; PK = pharmacokinetic; OLE = open-label extension; VIIS = Visual Index for Ichthyosis Severity; WOCBP = women of childbearing potential

a. Subjects will sign the OLE ICF at the Double-blind Day 90/Week 12 Visit or within 7 days thereafter. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing and PK from Day 90/Week 12 will be carried over for the OLE and will not be repeated.
b. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
c. IGA: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe
d. VIIS scale for each body area: chest/abdomen, back, legs, and arms, for a possible overall score = 16.
e. Roughness (0-4 scale); fissuring assessment on palms/soles: present/absent/number/pain (0-3 scale).
f. Subjects must be fasting (at least 8 hours)
g. Samples for PK will be drawn from all subjects at Day 120 and Day 180. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.
h. Subjects must record days/times of study drug application in the diaries and any areas of skin not treated (e.g., due to local reactions).
i. All subjects in the OLE will receive trifarotene 200 µg/g. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug tubes before dispensing. Dispense enough additional study drug until the next visit (except at Day 180).
j. Confirm study drug compliance by measuring tube weight and reviewing diary.

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

3.2. List of In-Text Figures

REASONS FOR AMENDMENT

Protocol Amendment 2 is a major amendment that addresses feedback from the Regulatory Agencies, Competent Authorities, Central Ethics Committees, and investigators. The following changes were made:

1. Changed the primary endpoint to the Investigator's Global Assessment (IGA) and made the Visual Index for Ichthyosis Severity (VIIS) a secondary endpoint.
2. Aligned power calculation and parameter assumptions with the new primary endpoint.
3. Added optional photography evaluation of scoring by a central reader who is not a study investigator as a quality check.
4. Clarified body areas that should be excluded from treatment and/or assessment, and clarified dose adjustment for local tolerability and documentation thereof.
5. Clarified inclusion and exclusion criteria, and added that subjects with recent systemic malignancy (e.g., within 5 years) are excluded, with exceptions for those with nonmelanoma skin cancer or cervical intraepithelial neoplasia Grade 1 who are >6 months post-treatment.
6. Added exclusion criteria for subjects unable or unwilling to stop use of topical or systemic retinoids; institutionalized subjects, and subjects in any way related to the sponsor, investigator, or site personnel.
7. Specified when the data safety monitoring board (DSMB) will meet and what data will be reviewed.
8. Added characterization of the investigational product.
9. Added background information about Study RD.03.SRE.40181E with CD5789 in subjects with ichthyosis.
10. Added rationale for 200 µg/g dose in OLE.
11. Added risk of absorption.
12. Added protective measures for risk of photosensitivity.
13. Specified that a tool will be supplied to apply investigational product to the back, and that if the investigational product (IP) is applied to the subject by someone other than the study subject, they should attend the first visit to learn how to apply it, and that hands must be washed immediately afterward or vinyl gloves should be used.
14. Specified windows and procedures for preventing blood draw contamination by the IP.
15. Specified that fissuring assessment is limited to palms/soles.
16. Added washout durations for keratolytics and monoclonal antibody medications, specified that washout includes physical treatments such as balneotherapy, and clarified that washout must be completed before study treatment begins.
17. Clarified that subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers.
18. Clarified that hormonal contraceptives must inhibit ovulation, and that abstinence relates to heterosexual intercourse and must be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
19. Revised the statistical analyses to reflect the change in endpoints.

20. Clarified permitted and prohibited therapies and medications, and use of standard of care treatment and timing thereof.
21. Specified that lamellar ichthyosis (LI) assessments must be done in order of presentation.
22. Revised descriptions of LI assessment tools scores (IGA and VIIS).
23. Defined fissures.
24. Clarified that investigators should use their judgment as to which quality-of-life tools should be used based on the subject's maturity.
25. Added a new section describing the photographic substudy.
26. Added electrocardiogram (ECG) for subjects in the PK substudy during serial blood draws on Days 1 and 30.
27. Clarified eligibility for OLE.
28. Reordered sections to put assessments in order of performance and renumbered all sections and lists accordingly.
29. Corrected duplicate endnote reference and typographical errors.

SUMMARY OF AMENDED SECTIONS

Section	Previous Text	Revision	Rationale
Synopsis and Section 7.1	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3-4 on a 5-point Visual Index for Ichthyosis Severity (VIIS) for scaling where 0 = clear and 4 = severe on at least 2 areas of the 4 body areas assessed (chest/abdomen, back, arms, and legs).	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point **Investigator Global Assessment [IGA)]** scale where 0 = clear; **1 = almost clear; 2 = mild; 3 = moderate;** and 4 = severe).	To follow FDA recommendation to use IGA as primary endpoint
Synopsis and Section 7.1	After the initial 15 subjects complete at least 28 days of treatment, an independent Data Safety Monitoring Board (DSMB) will review aggregate safety and tolerability data.	After the initial 15 subjects complete at least 28 days of treatment, an independent Data Safety Monitoring Board (DSMB) will review aggregate safety and tolerability data **(including PK and electrocardiogram [ECG] data).**	To clarify what data the DSMB will review
Synopsis and Section 7.1	All subjects who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE Period.	All subjects **(Cohort A and Cohort B)** who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE.	To specify that subjects from both double-blind cohorts will be eligible to continue into the Open-label Extension (OLE).
Synopsis, Table 2-1, Sections 7.1, Section 9.8, and 10.2.1.2	After Screening, eligible subjects for Cohort A and B will enter a Washout Period of up to 35 days, during which they must stop using the following prohibited medications	**Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods, as applicable. Washout may be up to 3 months, as necessary**	To allow for full washout of any prohibited medications before randomization. Therapeutic baths can substantially improve scaling and affect the IGA evaluation.

Section	Previous Text	Revision	Rationale
		Added: **During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.** **After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.**	For psychosocial and functional reasons, and to not deter them from entering the study, allow subjects to use usual care on visible skin and on hands and feet. To exclude bathing to better assess moderate to severe LI and evaluate IGA on rest of body. To ensure subjects complete screening and eligibility within 35 days of randomization after any necessary washout.
Synopsis and Table 9-1		**Added a washout period of 2 weeks** for topical keratolytics (e.g., urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo. **Added a washout period for monoclonal antibody treatment (e.g., anti-IL17) of 5 half-lives.**	To clarify length of the washout periods for these treatments.
Synopsis, Section 7.1, and Section 9.2	Thereafter, each subject will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of product in a tube. Subjects will record the date and time of study treatment administration in the subject diary.	Added: **If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.** **Subjects with heavy facial hair should not apply IP to hair-bearing areas.**	To specify areas not to be treated.

Section	Previous Text	Revision	Rationale
Synopsis		Added: **If the treatment causes application site reactions, the frequency of application will be reduced or interrupted only on the area concerned, as indicated herein.**	To clarify dose adjustment and evaluation.
Synopsis, Table 2-1 footnote, and Section 9.4	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for stinging/burning, pruritus, erythema) and the following procedures will be followed:	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for stinging/burning, pruritus, erythema) **for each body area (chest/abdomen, back, arms, legs, and face/neck)** and the following procedures will be followed:	To clarify areas to be assessed for local tolerability.
Synopsis and Section 9.4	– If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on this area only once weekly, until the score is back to <2. – If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3.	– If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area **(e.g., the face)**, the study drug will be applied on this area only once weekly, until the score returns to <2. **Continue to treat all other areas twice weekly provided the score is <2 on those areas.** – If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 **(i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas.** **Any changes in dosing must be documented in the subject diary and the eCRF.**	To clarify dose adjustment for local tolerability, and how it should be documented.

Section	Previous Text	Revision	Rationale
Synopsis and Section 7.1, and Section 10.3.1.9	Photographs will be taken at Baseline, Day 30 and Day 90 at selected sites with photographic capability for subjects who sign a separate photographic informed consent form (ICF).	**At all sites with photographic capability** photographs will be taken **as source data to support scoring** at Baseline, Day 30, and Day 90. **A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will** sign a separate, **optional** photographic informed consent form (ICF).	To obtain photographic evidence, where possible, for confirmation of scoring consistency, as assessed by a central reader.
Synopsis and Section 7.1		Added: **Visits for PK must occur at least 24 hours after the last application of the study drug, to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.**	To ensure pharmacokinetic (PK) blood draws are not contaminated with IP.
Synopsis and Section 7.1	In addition, a PK substudy will be conducted at specific sites with the capability to conduct it.	In addition, a PK substudy will be conducted **on Days 1 and 30 at sites with the capability to conduct it.** Added: **For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30.**	To clarify on which days the PK substudy will be performed, and that postdose ECGs will be performed during serial sampling on those days (per MHRA request).
Synopsis and Section 8.2.1	Inclusion criterion #3: Subject has moderate to severe (VIIS 3-4) LI on at least 2 of the 4 body areas assessed (chest/abdomen, back, arms, and legs).	Inclusion criterion #3: Subject has moderate to severe (**IGA 3-4**) LI on **the IGA** of LI severity.	To follow FDA recommendation to change primary endpoint to IGA.

Section	Previous Text	Revision	Rationale
Synopsis and Section 8.2.1	Inclusion criterion #7: • combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline OR Agrees to abstain from sex during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study.	Inclusion criterion #7: • combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline**; hormonal contraceptives must inhibit ovulation** • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline OR Agrees to abstain from **heterosexual intercourse** during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. **Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.**	To align with Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials, per MHRA.
Synopsis and Section 8.2.2	Exclusion criterion #2: Subject has a history of or current moderate or severe stinging/burning at Screening.	Exclusion criterion #2: Subject has ~~**a history of or**~~ current moderate or severe stinging/burning at Screening.	To clarify that history of stinging/burning does not prevent enrollment.
Synopsis and Section 8.2.2	Exclusion criterion #4: Subject with a known lipid disorder unless well controlled by stable doses of lipid-lowering agents for at least 6 months.	Exclusion criterion #4: Subject with a known lipid disorder **(hypertriglyceridemia >200 mg/dL, hypercholesterolemia >250 mg/dL)** unless well controlled by stable doses of lipid-lowering agents for at least 6 months.	To group all lipidema criteria together.

Section	Previous Text	Revision	Rationale
Synopsis and Section 8.2.2	Exclusion criterion #5: Subject was previously treated with trifarotene/CD5789, including the acne formulation, or participated in previous studies for ichthyosis.	Exclusion criterion #5: Subject was previously treated with trifarotene/CD5789 **in an acne or ichthyosis study.**	To avoid restricting enrollment.
Synopsis and Section 8.2.2	Exclusion criterion #6: Subject has known skeletal disease, hypertriglyceridemia, hypercholesterolemia, liver disease, or other poorly controlled medical conditions.	Exclusion criterion #6: Subject has **any other significant concomitant disease**, or poorly controlled medical **condition other than LI that, in the investigator's opinion, may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments**.	To add hypertriglyceridemia and hypercholesterolemia as exclusion criteria and combine Exclusion Criterion #4 and Exclusion Criterion #7 to avoid restricting enrollment
Synopsis and Section 8.2.2	Exclusion criterion #7: Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome), Crohn's disease, or any other significant concomitant disease other than LI that, in the investigator's opinion, may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments	Exclusion criterion #7: Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, **Cushing syndrome, Crohn's disease, or ulcerative colitis).**~~any other significant concomitant disease other than LI that, in the investigator's opinion, may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments~~	To exclude subjects with conditions that may affect skeletal integrity.
Synopsis and Section 8.2.2	Exclusion criterion #8: Subject is being treated for major depression disorder	Exclusion criterion #8: Subject is being treated for major depression disorder **and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts.**	To define major depressive disorder and to allow subjects with treated mild depression to be enrolled.

Section	Previous Text	Revision	Rationale
Synopsis and Section 8.2.2	Exclusion criterion #10: Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory b. Triglycerides >200 mg/dL c. Total cholesterol >250 mg/dL d. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women e. Platelets <150 × 10^9/L or >400 × 10^9/L	Exclusion criterion #10: Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory **b. Total bilirubin >1.1 mg/dL or, in case of Gilbert's syndrome, total bilirubin >3 mg/dL** c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women d. Platelets <150 × 10^9/L or >400 × 10^9/L	Moved triglycerides and total cholesterol to Exclusion Criterion #4 and add total bilirubin and Gilbert's syndrome (per MHRA request).
Synopsis and Section 8.2.2		Added**:** Exclusion criterion #12: **Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment.**	To exclude subjects with recent systemic malignancies.
Synopsis and Section 8.2.2		Added**:** Exclusion criterion #17: **Subject is unable or unwilling to stop use of topical or systemic retinoids**.	To exclude subjects using topical or systemic retinoids, per MHRA request.
Synopsis and Section 8.2.2		Added: Exclusion criterion #20: **Subject is institutionalized** Added: Exclusion criterion #21: **Subject is in any way related to the sponsor, investigator, or site personnel.**	To exclude vulnerable or biased subjects

Section	Previous Text	Revision	Rationale
Synopsis, Section 7.1, and Section 10.3	Primary efficacy endpoint: The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0-4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs).	Primary efficacy endpoint: The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear **on treated areas and at least a 2-grade change** from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period **on the 5-point IGA full body scale.**	To follow FDA recommendation to change primary endpoint from VIIS to IGA.
Synopsis and Section 13.1.4.1	The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear on treated areas and at least a 2-grade change from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA full body scale. The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0 4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs). Secondary endpoints: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices:	The **proportion** of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear on treated areas and at least a 2-grade change from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA full body scale. Secondary endpoints: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices **from baseline through Week 12**: – **5-point Visual Index for Ichthyosis Severity (VIIS) scale for scaling from Baseline through Week 12 (overall 16 points for scaling, i.e. 0-4 points for 4 body areas: chest/abdomen, back, arms and legs)** – Individual score for roughness (Scale: 0–4) overall – Palm/sole Assessment (Scale: 0–4)	To reflect change in endpoints; IGA is now primary endpoint (and thus, no individual scaling score is needed), and VIIS is a secondary endpoint. To limit fissure evaluation to the palms/soles. To clarify endpoints for statistical analysis.

Section	Previous Text	Revision	Rationale
	– Palm/sole Assessment (Scale: 0–4) – Individual score of scaling (Scale: 0–4) – Individual score for roughness (Scale: 0–4) overall • The difference in proportion of subjects with presence of fissures (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) between the active trifarotene cream HE1 and vehicle groups. • Quality of life per EQ-5D-5L • The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups • Quality of life per DLQI	– Quality of life per DLQI • The difference in proportion of subjects with presence of fissures **on palms/soles** (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) **at Week 12** between the active trifarotene cream HE1 and vehicle groups. • The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups **from Baseline through Week 12** • The **difference in quality** of life per EQ-5D-**5L** scores **between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12**	
Synopsis	Safety endpoints: • Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs • Local tolerability (Scale: 0-3 [none, mild, moderate, severe], determined by the investigator)	Safety endpoints: • Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs • Local tolerability (Scale: 0-3 [none, mild, moderate, severe], determined by the investigator) **for each body area (chest/abdomen, back, legs, arms, and face/neck).**	To clarify that tolerability will be assessed on all body areas where the treatment is applied.
Synopsis and Section 13.1.4.2	The intent-to-treat (ITT) population will comprise all randomized subjects. The modified intent-to-treat (mITT) population comprises all subjects in the safety	The intent-to-treat (ITT) population will comprise all randomized subjects. **This population will be used as the primary population for the analysis of efficacy for the**	To clarify that the intent-to-treat population will be used for the primary analyses of efficacy for the double-blind period.

Section	Previous Text	Revision	Rationale
	population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT in the Double-blind Period will be presented. Generalized estimating equations (GEE) for binary response will be used to model the odds of successful resolution of LI with treatment group as a predictor. Other covariates, such as baseline IGAVIIS scores, baseline characteristics, and interactions may be included. Various correlation matrix structures will be explored to model the within subject correlation. Additionally, the difference in mean VIIS score at Week 12/EOT between the active trifarotene cream HE1 groups and vehicle group will be analyzed using a 2-sided, 2-sample Wilcoxon rank-sum test at the 5% significance level; 95% confidence intervals will be presented. The VIIS scores as well as secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Week 24.	**Double-blind Period of the study.** The modified intent-to-treat (mITT) population comprises all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. The number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT in the Double-blind Period will be presented. **The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group, 95% CIs for the differences, and P-values for the differences in treatment will also be presented.** The **IGA** scores as well as **continuous** secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Week 24. Deleted: Frequencies of results and 95% confidence intervals will also be reported, and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test.	To follow change in primary endpoint and addition of secondary endpoints.

Section	Previous Text	Revision	Rationale
Synopsis and Section 10.1.1	Screening and washout: Up to 35 days	Screening: Up to 35 days **(after signing informed consent, if necessary, washout may be up to 3 months, and subjects should return to the site after washout to complete the study eligibility requirements)**	To allow for full washout of any prohibited medications before randomization.
Synopsis and Section 13.2	Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) using a 2-sample t-test assuming a mean difference of at least 1.0 and a standard deviation of 1.4 or lower.	Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) **using a 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively.**	To align power calculation and parameter assumptions with the new primary endpoint.
Table 2-1	Screening (-35 days to -1 day)	Screening (-35 days to -1 day) **Washout up to 3 months** **Added footnote a: Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods, as applicable. Washout may be up to 3 months, as necessary. During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower but not bathe or swim during the Screening Period. After completing any necessary**	To allow for full washout of any prohibited medications before randomization.

Section	Previous Text	Revision	Rationale
		washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.	
Table 2-1	Schedule of Events for Double-blind Period	Reordered assessments of IGA, VIIS, and roughness to be in order of conduct. Added **"palm/sole"** to fissuring assessment. Changed "assign randomization number" to "**Randomization via IWRS**." Added "**and sunscreen**" to advice on emollient use. Changed complete physical examination to be done at Screening and limited physical examinations at other time points as indicated. Changed height, weight, and BMI to be done at Screening instead of Baseline. Added abbreviation IWRS and definition. Added to footnote: Photography will be performed at sites with the capability for subjects who sign a photographic ICF. **A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check.** Added to footnote **subjects in PK substudy will have postdose ECG at each serial blood draw on Day 1 and Day 30**. Added to footnote: **Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the**	To clarify that IGA should be performed first and all efficacy assessments should be performed in the order in which they are listed within the protocol. To limit fissure evaluation to the palms/soles. To specify that randomization will be conducted via IWRS to avoid confusing site personnel. To include sunscreen to instructions regarding emollient use. To clarify when physical examinations and height, weight, and BMI are performed. To specify that a central reader will assess the photographs as a quality check of scoring consistency from Days 30 and 90. To ensure postdose ECGs are collected (per MHRA advice) for subjects in PK substudy during serial sampling. To ensure PK samples are not contaminated by recent application of study drug.

Section	Previous Text	Revision	Rationale
		skin after the last application.	
Table 2-2	Schedule of Events for Open-label Extension	**Revised footnote to IGA criteria**. Reordered and revised assessments	To specify order of assessment performance and that assessment of scaling is no longer done, and to clarify that fissuring only applies to palms/soles.
Section 5.2		Added: **One study was conducted with CD5789 50 µg/g, 100 µg/g, and placebo in subjects with icthyosis (Study RD.03.SRE.40181E). Among 31 subjects treated in this study, 17 were treated with CD5789 100 µg/g, and 14 were treated with 50 µg/g (all subjects received placebo [vehicle] on the contralateral zone). Mean (SD) baseline IGA score was 5.7 ± 1.6 among the 31 subjects. Improvement in the investigator's global assessment (IGA) of scaling and roughness was observed by Day 8 with both doses. The primary efficacy criterion was the change in IGA from the Baseline Visit (Day 1) to the Final Visit (Day 43). At Endpoint (intent-to-treat population, last observation carried forward [LOCF]), the CD5789 100 µg/g group had a statistically significant decrease from Baseline in IGA compared with Vehicle (-1.4±2.2; p=0.018) (Investigator's Brochure for CD5789 Cutaneous Formulation).** Added: **However, it is possible that absorption in subjects with LI may be greater than in healthy**	To add experience with CD5789 in subjects with ichthyosis and to clarify that systemic absorption may differ in subjects with ichthyosis.

Section	Previous Text	Revision	Rationale
		volunteers, due to the skin being compromised. **Based on these data, both the 100 µg/g and 200 µg/g doses showed an acceptable safety profile and will be used in this phase 2 LI study, to determine which of the 2 doses is most effective. The open-label extension (OLE) will evaluate the long-term safety of the higher dose in this patient population.**	
Section 5.3	The potential risks of study participation include those associated with exposure to tifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture.	The potential risks of study participation **for all subjects** include those associated with exposure to trifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture. Added: **In addition, subjects should take protective measures such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet), and/or seeking shade or shelter from the sun.** Added: **No clinically significant systemic risks associated with CD5789 have been identified. Given the mechanism of action for CD5789 Cream HE1, it is assumed that efficacy will increase as the dose is increased. As such, the 200 µg/g dose was selected for the OLE based on its previously established safety profile, expected superiority to placebo and 100 µg/g. However the Data Safety Monitoring Board (DSMB), who will routinely review aggregate safety and tolerability data, as well as any safety concerns brought**	To specify protective measures for avoiding sunlight/UV light (per MHRA request). To include systemic risks, and to add that the DSMB applies to both parts of the study and that if the 200 µg/g dose causes safety issues, the protocol will be amended if necessary.

Section	Previous Text	Revision	Rationale
		to the their attention by the study investigators or medical monitor, may determine that the study should be modified, placed on hold, or stopped if serious safety issues are discovered. This is applicable for both the double-blind portion and OLE. If the 200 µg/g dose in raises any safety concerns, the protocol will be amended and the dose will be reduced.	
Section 7.1	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe**])** averaged over the BSA and will follow the procedures detailed in Section 9.4	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) **for each treated body area (chest/abdomen, back, legs, arms, and face/neck)** and will follow the procedures detailed in Section 9.4	To clarify that local tolerability assessments will be performed on all treated areas.
Figure 7-1		Redrawn	Removed extraneous arrows; improved layout
Section 8.4	An investigator may discontinue a participant's study treatment for any of the following reasons • If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant	An investigator **must** discontinue a participant's study treatment for any of the following reasons • If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would **result in a significant burden to** the participant	To clarify that this is mandatory. To clarify that these would be burdensome to the participant.
Section 9.1		Added: **It is a potent RARγ agonist characterized by its high specificity to this receptor.**	To further characterize the investigational product.

Section	Previous Text	Revision	Rationale
Section 9.2		Added: **The IP should be applied thinly and gently rubbed in.** Added: **If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.**	To clarify how IP should be administered. To clarify that anyone other than the study subject, who may apply the IP to the subject, is trained on application of IP.
	Subjects should not apply IP on visit days until after the visit.	Added: **Persons other than the study subject applying the study drug must wash their hands after application or use disposable vinyl gloves. In addition, a long-handled applicator will be provided for application on the back. The applicator must be washed with warm water and soap after every application.** **Trifarotene cream should not come into contact with the eyes, mouth, angles of the nose, or mucous membranes. For the ectropion treatment, Q-tips are recommended for precise application on eyelids, without contact to the eye or conjunctiva. If the IP gets into the eye, it must be flushed immediately with warm water. In case of eye irritation, the subject must be seen by an ophthalmologist.**	To specify areas not to be treated. To ensure the safety of others who may apply the IP to the study subject and to improve application. To ensure PK blood draws are not contaminated with IP.

Section	Previous Text	Revision	Rationale
		At least 24 hours must have elapsed since last IP administration before PK blood draws are performed. Subjects should not apply IP to the area where blood will be drawn for at least 24 hours before the next PK sample draw. Subjects should not apply IP on visit days until after the visit, **unless they are participating in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the blood draw. Among subjects participating in the PK substudy, ensure the PK line is inserted before study drug application to prevent contamination with the IP and protect the skin around the needle insertion point from study drug application.**	
Section 9.3		Added: **Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application. Subjects should not apply the IP on visit days until after the visit, unless they participate in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the PK blood draw.**	To ensure PK blood draws are not contaminated with IP.
Section 9.4.1		Added: **Any changes in dosing must be documented in the subject diary and the eCRF.**	To ensure documentation of any dosing changes.

Section	Previous Text	Revision	Rationale
Section 9.5		Added: **Subjects who taper to once weekly application or who take a "drug holiday" for tolerability will not be reported as having deviated from the protocol (see Section 9.4 for dose adjustment and stopping rules); any changes in dosing must be documented in the subject diary and the eCRF.**	To clarify that subjects who require dose adjustment because of local tolerability will not be counted as having deviated from the protocol.
Section 9.7	Unblinding should be discussed in advance with the medical monitor, if possible.	**The investigator may discuss with the medical monitor in advance of unblinding a subject,** if possible, **if it is not deemed as an emergency**. **However, the investigator has the ultimate decision for unblinding a subject for medical treatment and no procedures will prevent or delay necessary unblinding in an emergency for the subject's safety**.	To clarify that the investigator has the authority to make decisions about unblinding a subject (per MHRA recommendation).
Section 9.8.1	Subjects will be advised on permitted emollient(s) for use on nontreatment days during the study; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited.	Subjects will be advised on permitted emollient(s) for use **as often as needed** on nontreatment days during the study**; on treatment days, the use of emollient(s) is permitted except within 4 hours before or after study drug application. Similarly, protective sunscreen should be applied as often as needed, except within 4 hours before or after study drug application. Subjects may use their standard of care treatment on their faces and/or palms/soles after the Week 4 assessment if they experience a worsening of IGA in those areas. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. These standard of care treatments should be approved by the investigator and documented in the eCRF.**	To clarify when use of emollients and protective sunscreen is permitted. To add sunscreen as protection from sunlight/UV light. To allow subjects who experience worsening of IGA to return to standard of care treatment, as approved by the investigator, after Day 30. To avoid combination treatment during the OLE (no washout is necessary). Standard of care is permitted after the OLE Week 16 visit, as long as it does not contain prohibited medications,

Section	Previous Text	Revision	Rationale
		Subjects who enter the OLE must stop standard of care treatment. If they experience a worsening of IGA they may use standard of care treatment on their faces and/or palms/soles after the Week 16 visit if the standard of care does not contain prohibited medications. If those standard of care treatments include prohibited medications, the subject should be discontinued from the study.	
Section 9.8.2	The therapies listed in Table 9-1 are prohibited during the study.	The **medications** listed in Table 9 1 are prohibited during the study. Added: **Balneotherapy is also prohibited during the Screening Period and during the study.** Added: **Use of benzoyl peroxide is permitted on non-treatment days for subjects with concomitant acne only; it must not be applied on treatment days due to risk of inactivation of trifarotene by benzoyl peroxide.** Added: **For enrolled subjects who require prescription of a systemic azole, the principal investigator should discuss with the medical monitor whether the subject may continue in the study.**	To allow subjects with acne to use benzoyl peroxide on nontreatment days. To specify that physical treatments such as balneotherapy are also prohibited. To specify that if subjects are prescribed an azole after study enrollment, their continued participation must be discussed with the medical monitor.

Section	Previous Text	Revision	Rationale
Section 9.8.3	Subjects should not shower, bathe, or swim within 4 hours of after study drug application. No occlusive dressings should be applied to areas where study drug was applied. Subjects should only use investigator-approved emollients, and should not use them on treatment days within 4 hours of study drug application.	Subjects should not shower, bathe, or swim **for at least** 4 hours after study drug application. No occlusive dressings should be applied to areas where study drug was applied. Subjects should only use investigator-approved emollients, and should not use them on treatment days **for at least** 4 hours **before and after study drug** application. Added: **In addition, subjects should take protective measures to avoid exposure of treated areas to sunlight, such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet), and/or seeking shade or shelter from the sun.**	To clarify the window for showering or bathing and use of emollients on treatment days. To improve safety with regard to exposure to sunlight/UV light.
Section 10.2		Added: **It is suggested that quality of life assessments be conducted first to avoid any bias, and that the IGA be recorded as the first LI assessment at every visit.**	To clarify order of assessment and to ensure IGA is recorded first as primary efficacy endpoint.
Section 10.2.1.1	Subjects must be screened within 35 days before randomization in the study. The following procedures will be performed at Screening	The subject must **complete eligibility screening** within 35 days before randomization in the study. The following procedures will be performed **during** Screening Reordered assessments to be in order of performance**.** Revised assessments to exclude individual scaling, to limit fissuring to palms/soles, and to add photographs as source documents**.**	To reflect that subjects who require washout may return to the site to complete eligibility assessments within 35 days of randomization. To reflect the changes in primary and secondary endpoints, the limit of fissuring to palms/soles, and the addition of photographs as source documents, and to ensure the order of assessments is correct.
Section 10.2.2.1		Reordered assessments to be in order of performance.	To specify order of assessments; to specify that randomization is via

Section	Previous Text	Revision	Rationale
		Revised assessments to exclude individual scaling, to limit fissuring to palms/soles, and to add cross-reference to Sections 10.3.1.5 and 10.3.1.6. Specified randomization to be done via IWRS. Added caution to **ensure that PK lines are placed before IP application**. Added instructions **if the product will be applied at home by someone other than the study subject.** Added **sunscreen(s**) use on nontreatment days and time frame for use on treatment days. Added: **Among subjects in the PK study, perform an additional ECGs at times of serial sampling.**	the IWRS,; to specify that fissuring is only to be assessed on palms/soles, to provide location of specific quality of life scales, to specify procedures and times for PK serial blood draws to prevent contamination with IP, to ensure persons other than the study subject who may apply IP to the study subject are trained in IP application procedure; and to specify when emollients and protective sunscreen may be used on treatment days.
Section 10.2.2.2 and Section 10.2.2.5	Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit.	Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) **and/or sunscreen(s)** on study drug treatment days within 4 hours **before or after** study drug application is prohibited), and remind subjects **that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should** not apply IP on visit days until after the visit.	To specify when emollients and protective sunscreen may be used on treatment days, and to add a window for IP application before next visit to prevent IP-contamination of PK blood samples.
Sections 10.2.2.3, 10.2.2.4, 10.2.2.6, and 10.2.2.7		Reordered assessments to be in order of performance. Revised assessments to exclude individual scaling, to **limit fissuring to palms/soles**, and to add cross-reference to Sections 10.3.1.5 and 10.3.1.6. Added **sunscreen(s)** use on nontreatment days and time frame for use on treatment days.	To specify order of assessments; to specify that fissuring is only to be assessed on palms/soles; to provide location of specific quality of life scales; to specify when emollients and protective sunscreen may be used on treatment days, and to add a window for IP

Section	Previous Text	Revision	Rationale
		Added reminder that **24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.**	application before next visit to prevent IP-contamination of PK blood samples.
10.2.2.4		Added caution to **ensure that PK lines are placed before IP application.** Added: **Among subjects in the PK study, perform an additional ECGs at times of serial sampling.**	To specify order of assessments; to specify that fissuring is only to be assessed on palms/soles; to provide location of specific quality of life scales; to specify procedures and times for PK serial blood draws to prevent contamination with IP; to add postdose ECGs for subjects in PK substudy; and to specify when emollients and protective sunscreen may be used on treatment days.
Section 10.2.2.7	For subjects who successfully complete the initial 12 weeks of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study.	For subjects who successfully complete **(i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion)** the initial 12 weeks of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study.	To define "successful completion" of the Double-blind Period and to clarify eligibility for OLE.
Section 10.2.4	Subjects who complete the 12-week Double-blind Treatment Period of the study may choose to continue into an optional 12-week Open-label Extension with trifarotene cream HE1 200 µg/g.	Subjects who **successfully** complete **(i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion)** the **initial 12 weeks of double-blind treatment** may choose to continue into an optional 12-week OLE with trifarotene cream HE1 200 µg/g.	To clarify eligibility for OLE.

Section	Previous Text	Revision	Rationale
Section 10.2.4.2 – 10.4.2.7		Reordered assessments to be in order of performance, and revised assessments to **limit fissuring to palms/soles**. Added **sunscreen(s)** use on nontreatment days and time frame for use on treatment days. Added reminder that at least **24 hours must have elapsed since IP application before the subject's next PK blood draw**.	To specify order of assessments; to specify that fissuring is only to be assessed on palms/soles. To specify when emollients and protective sunscreen may be used on treatment days. To add a window for IP application before next visit to prevent IP-contamination of PK blood samples.
Section 10.3	The 5-point VIIS is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. The VIIS scale was developed to generate a reliable method to assess ichthyosis clinical severity using solely scale and erythema, which are the only findings present in ichthyosis of every genetic cause, and occur either upon skin of normal thickness (lamellar subtypes) or upon thickened skin (keratoderma subtypes).[13] The VIIS uses a 5 point index to assess the level of severity of scale and erythema in each of 4 body areas: chest/abdomen, back, legs, and arms, for a possible overall total of 16 points (Section 10.3.1.1).	The 5-point **IGA** is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. **The IGA scale was developed with the support of experts from academic reference centers for the treatment of ichthyosis. Each level of severity will consider both the severity of scaling and the severity of roughness** (Section 10.3.1.1).	To reflect the change in primary endpoint to IGA.
Section 10.3.1.1	10.3.1.1 Visual Index for Ichthyosis Severity – Scaling The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/EOT on	10.3.1.1 **Investigator's Global Assessment** The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear **and at least a 2-grade change from Baseline at Week 12/EOT in the Double-blind Period on**	To reflect the change in primary endpoint to IGA and that fissuring will only be assessed on palms/soles.

Section	Previous Text	Revision	Rationale
	the overall 16-point VIIS for scaling. The investigator will rate the subject's condition using the 5-point VIIS for each body area (chest/abdomen, back, legs, and arms) and an overall score at each time point shown in the Schedule of Events (Section 2.2): 0 Clear Normal skin; no perceptible scale or smoothening 1 Almost clear Areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum) 2 Mild Confluent smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum) 3 Moderate Confluent scales (visibly separated/fractured stratum corneum) including some large (>1cm), thick scales 4 Severe Confluent, primarily large, thick scales	**the 5-point IGA full body scale.** The investigator will rate the subject's condition using the 5-point **IGA** at each time point shown in the Schedule of Events (Section 2.2). **The IGA will be measured on a 5-point scale, excluding the following areas: knees, elbows, neck, palms, soles, axillae, groin, and scalp**: 0 Clear **No scaling and no roughness** 1 Almost Clear **Occasional fine scales; hardly palpable roughness (mostly smooth**) 2 Mild **Small and fine scales predominate; no more than a few large scales; mild roughness on palpation** 3 Moderate **Some large scales that may be thick; coarse roughness on palpation** 4 Severe **Confluent, primarily large (>1 cm), thick scales with plate-like hyperkeratosis**	

Section	Previous Text	Revision	Rationale
Section 10.3.1.2	10.3.1.2 Investigator's Global Assessment	Changed to : 10.3.1.2 **Visual Index for Ichthyosis Severity – Scaling** The ~~primary~~ **secondary** endpoint is the number of subjects in each treatment group who experience a severity score of 0 or 1 ~~and at least a 50% reduction from Baseline~~ at Week 12/EOT on **the overall 16 point VIIS for scaling**. The investigator will rate the subject's condition using the **5-point VIIS for each body area (chest/abdomen, back, legs, and arms)** and an overall score at each time point shown in the Schedule of Events (Section 2.2). Deleted **clear/almost clear/mild/moderate/severe** from scoring scale.	To reflect the change in primary endpoint to IGA.
Section 10.3.1.3	Individual Score of Scaling (Scale: 0-4)	Changed to: Individual Score **for Roughness**	No individual score for scaling is needed now that IGA is primary endpoint.
Section 10.3.1.5		Added: **A fissure is a longitudinal and deep crack that separates the stratum corneum and may penetrate down to the dermis, causing pain and sometimes bleeding.**	To clarify the definition of a fissure.
Section 10.3.1.8		Added: **Figure 10-1 Ectropion Severity Score** (from reference #14)	To show how the ectropion score should be calculated.

Section 10.3.3	Sample Collection: Blood: Each blood sample will be 3 mL/kg in volume. The total amount of blood to be drawn for serial PK assessments will be a maximum of 5 mL/kg per subject over a 24-hour period.	Added: **Finding veins in subjects with this disease can be challenging. Blood draws will be done at the corresponding study visits before application of the IP and should be 24 hours after IP application. Subjects must not apply the IP to the area where blood will be drawn within 24 hours before their next study visit to avoid contamination of the blood by IP that remained in the skin. For subjects in the PK substudy, a cannula should be placed before IP application and the cannula site may be occluded to prevent contamination with IP.** **Actual PK sample times for subjects in the PK substudy will be recorded in the eCRF.** Blood: **For subjects not in PK substudy:** **The expected amount of blood to be drawn at each visit varies from approximately 6 mL to a maximum of 21 mL (Screening Visit only). The total amount of blood drawn for the study will be about 123 mL per subject, unless the subject takes part in the PK substudy.** **For subjects in PK substudy:** **For subjects who opt to participate in the PK substudy, extra blood samples will be drawn at Visit 2 and at Visit 4 for PK analysis. The amount of blood to be drawn per subject at each of these visits will be approximately 54 mL. For subjects taking part in the substudy, the total amount of blood drawn for**	To clarify how blood draws should be performed to prevent contamination with IP.

Section	Previous Text	Revision	Rationale
		the entire study will be approximately 195 mL.	
Section 10.3.4.2.2		Added: **Gel ECG electrodes may be used for ECGs because they are more conductive and cause less trauma on compromised skin. Efficacy assessments should be conducted before ECGs to avoid possible artefact/changes from the ECG.** **For subjects in the PK substudy, additional ECGs will be performed postdose during serial blood sampling on Day 1 and Day 30.** **If there is a marked prolongation of the QT/QTc interval during treatment, a subject should be discontinued from the IP, but remain in the study until full resolution of the event. The DSMB will be informed immediately of such an occurrence.**	To ensure the most comfortable method is used; to address order of assessments; to add ECGs postdose at Day 1 and Day 30 (per MHRA request) among subjects in the PK substudy; and to address procedures should QT/QTc prolongation occur.
10.3.4.2.3	A complete physical examination excluding the genitourinary examination will be performed as indicated in the Schedule of Events (Section 2.2).	A complete physical examination excluding the genitourinary examination **will be performed at Screening, while limited physical examinations (to include HEENT, cardiorespiratory, abdomen, and range of motion)** will be performed as indicated in the Schedule of Events (Section 2.2).	To clarify when complete and limited physical examinations are to be performed.
Section 10.3.4.2.4	All application site reactions will be recorded as AEs.	All application site reactions will be recorded as **TE**AEs **in the diary. These should include the date and severity of the TEAE.**	To specify that all application site reactions should be recorded in the subjects' diaries in detail.
Section 11.2.3		Added: **Any AE that occurs during the Screening Period will be captured as such on the AE page of the eCRF (not medical history).**	To clarify that any AE that occurs after signing of the ICF is to be captured as such and not as medical history.

Section	Previous Text	Revision	Rationale
Section 11.3.2	All WOCBP who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation.	All WOCBP who participate in the study should be counseled on the need to practice **highly effective** birth control and on the importance of avoiding pregnancy during study participation. Added: **Among the clinical studies, 12 pregnancies were reported: 4 resulted in normal births; 5 resulted in spontaneous abortions (none of which was considered related to CD5789); 1 was electively aborted, and 2 were lost to follow-up (Investigator's Brochure for CD5789 Cutaneous Formulation).**	To clarify that birth control must be "highly effective" (per MHRA). To add data on pregnancy from clinical studies with CD5789.
Section 12	The DSMB will meet after subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data. The data will remain blinded unless an issue or trend arises that requires unblinding. At that time, the DSMB will decide whether Cohort B (adults and subjects aged 12–17) may begin enrolling. The DSMB will have the authority to recommend to the sponsor that the study be placed on hold, or discontinued if serious safety issues are discovered.	The DSMB will meet after **15** subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data **(including PK and ECG results)**. The **safety** data will **be un**blinded. At that time, the DSMB will decide whether Cohort B (adults and subjects aged 12–17) may begin enrolling, or if additional adult safety data are required before allowing subjects aged 12 – 17 to participate in the study. The DSMB will have the authority to recommend to the sponsor that the study be **modified**, placed on hold, or **stopped** if serious safety issues are discovered. Added: **Any protocol changes the DSMB may suggest will be submitted to all applicable regulatory bodies for review and approval.**	To clarify when the DSMB will meet, and what data they will review.
Section 13.1.2.2 and Section 13.1.3		Added: **Subjects who taper to once-weekly application or who take a "drug holiday" will not be reported as having deviated from the protocol.**	Clarified that subjects requiring dose adjustment or temporary interruption are not protocol deviators.

Section	Previous Text	Revision	Rationale
Section 13.1.2.3	Baseline subject characteristics will include medical history, physical examination findings, and **VIIS** score.	Baseline subject characteristics will include medical history, physical examination findings, and **IGA** score.	To reflect change in primary endpoint to IGA.
Section 13.1.4	The mITT population will be used as the primary population for the primary analysis of efficacy at Week 12. All efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE using the OLE mITT and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE.	The **ITT** population will be used as the primary population for the primary analysis of efficacy at Week 12. **Select** efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE using the **OLE ITT,** OLE mITT, and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE	
Section 13.1.4.2	Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from baseline will be provided for VIIS scores for both periods.	Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from baseline will be provided for **IGA** scores for both periods.	To reflect the change in primary endpoint to IGA.
Section 13.1.4.3	Additionally, for the Double-blind Period only, change from Baseline endpoints through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate. Frequencies of results and 95% CIs will also be reported and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test.	Additionally, for the Double-blind Period only, change from Baseline **in continuous secondary endpoints** through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate. Added: **The proportion of subjects with at least a 50% reduction in IGA score from Baseline will be analyzed using the same logistic regression analysis described in Section 13.1.4.2.**	To reflect and clarify changes in secondary endpoints.

Section	Previous Text	Revision	Rationale
Section 13.1.4.5	To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using LOCF for the Double-blind Period only. Imputation will not be performed in the OLD period.	To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using **multiple imputation (MI)** for the Double-blind Period only. **Multiple-imputations will be used to replace missing IGA outcomes using multiple draws from the posterior predictive distribution estimated from the treatment groups. IGA scores will be imputed and then categorized as treatment success according to Section 13.1.4.1. Imputation will not be performed in the OLE period. Full details will be specified in the Statistical Analysis Plan (SAP).** Added: **The proportion of subjects who experience a 2-grade change from baseline to Week 12 in individual score for roughness and palm/sole assessment will also be explored using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group and the 95% CIs for the differences will be presented.**	To align with current FDA thinking. Single imputation does not consider all missingness patterns. To explore a defined threshold for a clinically meaningful endpoint for phase 3.
Section 13.1.6.1	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) averaged over the BSA.	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) **for each treated body area (chest/abdomen, back, arms, legs, and face/neck).**	To clarify that all treated areas are included in the local tolerability assessment.

Section	Previous Text	Revision	Rationale
Section 14.7.2	Blood samples will be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed	Blood samples will be used for purposes related to **this study only, and will not be stored for future research**. The samples will be stored until **they are no longer needed**, and the decision has been made that none of the samples needs to be reanalyzed.	To clarify that no samples will be stored for future research

AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ATC	anatomical therapeutic chemical
AUC	area-under-the-curve
BMI	body mass index
BSA	body surface area
CFR	code of federal regulations
CI	confidence interval
C_{max}	maximum concentration
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressure
DLQI	dermatology life quality index
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end-of-treatment
ESS	ectropion severity score
FDA	Food and Drug Administration
GCP	good clinical practice
GEE	generalized estimating equations
HR	heart rate
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IND	investigational new drug
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat

ABBREVIATION	EXPLANATION
IUD	intrauterine device
IWRS	interactive web response system
LI	lamellar ichthyosis
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
MMRM	mixed model of repeated measures
NCA	noncompartmental analysis
OC	observed case
OLE	open-label extension
PG	propylene glycol
PK	Pharmacokinetic(s)
PoC	proof-of-concept
PP	per-protocol
QTc	QT interval corrected for heart rate
RARγ	retinoid acid receptor γ
RBC	red blood count
RR	respiratory rate
RXR	retinoid X receptor
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
TEAE	treatment-emergent adverse event
T_{max}	time of C_{max}
UAE	unexpected adverse event
UADR	unexpected adverse drug reaction
US	United States
UV	ultraviolet
VIIS	Visual Index for Ichthyosis Severity
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

5. INTRODUCTION

5.1. Background and Rationale

The ichthyoses comprise a large group of skin scaling disorders with diverse etiology. The stereotypic pathophysiology is epidermal hyperplasia and the formation of excess stratum corneum accompanied by abnormal (delayed and/or disordered) desquamation, with visible accumulation of squames (scales) on the skin's surface – the clinical hallmark of all the ichthyoses.

Lamellar ichthyosis (LI) is recognized as a severe form of ichthyosis that persists throughout life. During the first postnatal weeks, the hyperkeratotic membrane patients are typically born with is gradually shed, and is replaced by scaling and lichenification that involves the entire body including the intertriginous areas, palms, soles, and scalp. While usually not life threatening, LI can result in disability, partial deafness, poor adaptation to environmental conditions (due to hypohydrosis), severe discomfort (pruritus, fissuring of the skin) and significant psychosocial impact.

Lamellar ichthyosis, a member of the nonsyndromic autosomal recessive congenital ichthyosis group of ichthyoses, has an incidence of 1 per 100,000-300,000 live births.[1] Lamellar ichthyosis is undoubtedly a rare disease.

Therapeutic approaches for LI are mainly based on the use of topical emollients, keratolytic agents (urea, lactic acid, salicylic acid), topical retinoids and, in severe cases, oral retinoids.[2,3]

Oral retinoid usage in LI is mainly based on case reports and case series.[4,5,6,7,8] The mechanism of retinoid action involves modulation of keratinocyte differentiation, keratinocyte hyperproliferation and tissue infiltration by inflammatory cells. Systemic retinoids (such as acitretin, etretinate, or isotretinoin) have been found to be efficacious in the treatment of severe ichthyoses, especially in LI.[6]

Vahlquist, et al (2008)[3] report that by combining 2 or more keratolytic agents and moisturizers in the same lipophilic cream base, it is often possible to achieve additive or even synergistic effects in LI without the need to use irritating concentrations of either agent alone. In a double-blind trial of 4 different cream mixtures in 20 patients with LI, a mixture of 5% lactic acid and 20% propylene glycol (PG) in a semi-occlusive cream for 4 weeks twice daily was significantly more effective than 20% PG or 5% urea alone in the same vehicle.[9] Although the treatments were well tolerated, an efficient removal of hyperkeratosis without correcting the underlying biochemical defect in LI is likely to deteriorate the patient's intrinsic barrier problem, because an excessive production of corneocytes probably represents a homeostatic response to an ineffective barrier. Indeed, transepidermal water loss increased after successful treatment of LI with either topical keratolytics[9] or oral retinoid.[10] Although this may not be noticeable by the patient, even minor deteriorations in the barrier function can enhance transcutaneous penetration of active cream ingredients or other topically applied chemicals, which is a matter of special concern in children. Accordingly, α-hydroxy acids and salicylic acid should not be used at all in babies and only with great caution when treating large, eroded skin areas in adult patients.[11,12]

Many patients with LI use pumice, foot files, or gentle rubbing of the skin after a hot bath or a shower to remove scales and hyperkeratosis. Overnight occlusion of problematic skin areas with plastic sheets after applying a thick layer of emollient or keratolytic agents is another way of potentiating therapy, especially on the scalp, which is notoriously difficult to treat. Although

usually effective, all these remedies may further damage the skin barrier and lead to exaggerated epidermal proliferation, erythema, painful erosions and increased transcutaneous penetration.[3]

Based on this information, LI has significant unmet medical need for safer and more effective therapies.

5.1.1 CD5789 (Trifarotene)

CD5789 is a new chemical entity discovered by Galderma R&D SNC and formulated for topical application. It is a novel retinoid acid receptor γ (RARγ) agonist, characterized by its high specificity to this receptor. CD5789 is selective for RARγ over RARα and RARβ (approximately 50- and 8-fold, respectively), with no retinoid X receptor (RXR) activity. CD5789 is currently under clinical development for the topical treatment of various dermatoses, including acne vulgaris and LI.

The pharmacological retinoid-like properties of CD5789 were confirmed in in vitro and in vivo models, showing its interest for its development in the treatment of LI. Therefore, it may have an effect on the differentiation and hyperproliferation of keratinocytes, and consequently improve hyperkeratotic skin of patients with lamellar ichthyosis.

Within the overall acne development program at Galderma, CD5789 has been tested in different pharmaceutical forms for topical administration. As of 15-Jan-2018, 6 different formulations have been evaluated: a solution, a gel and 4 creams (CD5789 cream A, CD5789 cream B, CD5789 cream HE1 concept and its optimized version, cream HE1), with different concentrations (up to 400 µg/g). Therefore, several formulations at different CD5789 concentrations have been tested in nonclinical and clinical development programs.

Galderma decided to develop a new cream formulation that might better address the issue of skin dryness in patients with LI. This formulation was named “Cream HE1 concept.” It has been preliminarily investigated in an exploratory trial in psoriasis at concentrations up to 400 µg/g (RD.03.SRE.40204E). In a proof-of-concept study (RD.03.SRE.40181E), positive results were also obtained in patients with LI with CD5789 cream (up to 100 µg/g) that was effective in decreasing scaling and roughness. Based on these results, a new CD5789 formulation (cream HE1) was developed for further clinical investigations in LI. The formulation cream HE1 was developed with the objective to obtain a formulation with appropriate stability of the active ingredient and in which CD5789 would be homogeneously dissolved in the oily phase at a higher concentration compared to the cream formulation used in the acne program. Cream HE1 contains 100, 200, or 400 µg/g (0.01% [w/w], 0.02% [w/w], 0.04% [w/w], respectively) of CD5789.

Galderma has granted Mayne Pharma LLC an exclusive license to develop and commercialize CD5789 (trifarotene) for LI and other orphan diseases; therefore, the LI indication is no longer pursued by Galderma.

5.2. Clinical Experience

The cream HE1 differs from the CD5789 cream used to treat acne vulgaris in that it contains fewer excipients with drying effects and therefore may be better suited for patients with LI.

Throughout the 30 clinical studies that comprise the clinical development program for CD5789 topical products, 1976 subjects were exposed to CD5789. No systemic safety concerns related to CD5789 gel or creams, or cream HE1 at doses up to 400 µg/g were reported. The subjects were

exposed to a maximal total CD5789 dose of 36 g/day (Investigator's Brochure for CD5789 Cutaneous Formulation).

One study was conducted with CD5789 50 μg/g, 100 μg/g, and placebo in subjects with ichthyosis (Study RD.03.SRE.40181E). Among 31 subjects treated in this study, 17 were treated with CD5789 100 μg/g, and 14 were treated with 50 μg/g (all subjects received placebo [vehicle] on the contralateral zone). Mean (SD) baseline IGA score was 5.7 ± 1.6 among the 31 subjects. Improvement in the investigator's global assessment (IGA) of scaling and roughness was observed by Day 8 with both doses. The primary efficacy criterion was the change in IGA from the Baseline Visit (Day 1) to the Final Visit (Day 43). At Endpoint (intent-to-treat population, last observation carried forward [LOCF]), the CD5789 100 μg/g group had a statistically significant decrease from Baseline in IGA compared with Vehicle (-1.4±2.2; p=0.018) (Investigator's Brochure for CD5789 Cutaneous Formulation).

The CD5789 PK profile was also investigated using cream HE1 (Study GD.03.SRE.103813) in 36 healthy volunteers of Japanese and non-Japanese origin. Subjects were treated daily on up to 90% of body surface area (BSA) for 29 days with up to 36 g of cream formulation. Both CD5789 100 μg/g and 200 μg/g cream HE1 were investigated. Plasma PK assessment demonstrated that repeated topical applications of CD5789 cream HE1 resulted in low and similar CD5789 systemic levels in all treatment groups. In addition, no systemic safety concerns were raised from this healthy volunteer study in which cream HE1 200 μg/g was applied daily under maximal-use conditions on almost the full body. In this study, however, the level of irritation resulted in the need to decrease the frequency of application to twice weekly (Investigator's Brochure for CD5789 Cutaneous Formulation). However, it is possible that absorption in subjects with LI may be greater than in healthy volunteers, due to the skin being compromised.

Based on these data, both the 100 μg/g and 200 μg/g doses showed an acceptable safety profile and will be used in this phase 2 LI study, to determine which of the 2 doses is most effective. The open-label extension (OLE) will evaluate the long-term safety of the higher dose in this patient population.

5.3. Summary of Potential Risks and Benefits

Although the primary objective of this study is safety in the patient population with LI, the potential benefits of study participation are that subjects with LI may experience a reduction in their LI symptoms as a result of treatment with trifarotene (CD5789) cream HE1. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to trifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture.

Animal studies with CD5789 have shown reproductive toxicity in the embryo-fetal studies. Despite low systemic levels with the CD5789 concentration of 50 μg/g used in patients with acne, CD5789 must not be administered during pregnancy.

When CD5789 is used in the other formulations and/or for other indications and/or with higher concentrations or higher application surface areas, the potential risk of teratogenicity needs to be considered as the safety margin may be lower. Depending on the study population and conditions mentioned above, or other specific requirements, the appropriate contraception method is described in this protocol.

It is unknown whether CD5789 or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Lactating women are not eligible for the clinical study.

Certain cutaneous signs and symptoms of irritation and localized reactions at the application site such as erythema, scaling, dryness, stinging/burning, and pruritus may be experienced with use of CD5789. Depending upon the severity of these side effects, subjects may be instructed to reduce the frequency of application or to discontinue use.

Trifarotene cream contains propylene glycol that is mildly irritant to the skin, eyes, and mucous membranes. Trifarotene (CD5789) cream HE1 also contains butylated hydroxytoluene that may cause local skin reactions (e.g., contact dermatitis), or irritation to the eyes and mucous membranes and sodium benzoate that is mildly irritant to the skin, eyes, and mucous membranes.

CD 5789 is mildly irritant to the skin, eyes, and mucous membranes. Therefore, it should not come into contact with the eyes, mouth, or mucous membranes.

There is a potential risk of skin sensitization. If a reaction suggesting sensitivity to trifarotene (CD5789) cream HE1 occurs, the use of the trifarotene cream HE1 must be discontinued.

There is a potential risk of photosensitivity disorder (sunburn). Excessive exposure to sunlight or ultraviolet (UV) radiation (i.e., occupational exposure to the sun, planned holidays in the sun during the study, phototherapy, tanning salon) must be avoided during the studies. In addition, subjects should take protective measures such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet) and/or seeking shade or shelter from the sun.

As reported with other topical retinoids, there is a potential risk of pigmentation disorders.

No clinically significant systemic risks associated with CD5789 have been identified. Given the mechanism of action for CD5789 Cream HE1, it is assumed that efficacy will increase as the dose is increased. As such, the 200 µg/g dose was selected for the OLE based on its previously established safety profile, expected superiority to placebo and 100 µg/g. However the Data Safety Monitoring Board (DSMB), who will routinely review aggregate safety and tolerability data, as well as any safety concerns brought to the their attention by the study investigators or medical monitor, may determine that the study should be modified, placed on hold, or stopped if serious safety issues are discovered. This is applicable for both the double-blind portion and OLE. If the 200 µg/g dose in raises any safety concerns, the protocol will be amended and the dose will be reduced.

A summary of the pharmaceutical properties and known potential risks of trifarotene (CD5789) cream HE1 is provided in the current version of the investigator's brochure (IB). The investigator must become familiar with all sections of the trifarotene (CD5789) cream IB before the start of the study.

6. OBJECTIVES

6.1. Primary Objective

The primary objective is to compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in subjects with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 12 weeks of treatment.

6.2. Secondary Objectives

The secondary objectives are as follows:

- To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% BSA twice weekly.
- To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.

7. STUDY DESIGN

7.1. Overall Study Design and Plan

The first part of this study is a phase 2, randomized, 2-cohort, double-blind, vehicle-controlled, multicenter study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in subjects with LI. Subjects who complete the randomized, double-blind, vehicle-controlled period of the study will be eligible to continue into an open-label extension (OLE) and be treated with trifarotene cream HE1 200 µg/g for an additional 12 weeks.

The randomized, double-blind, vehicle-controlled period of the study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Investigator Global Assessment [IGA] scale where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe, is designed to compare the safety of 2 doses of trifarotene cream HE1 with that of vehicle in the treatment of LI.

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods (Table 9-1), as applicable. Washout may be up to 3 months, as necessary.

During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower, but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline. After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.

The first cohort of subjects (Cohort A) will randomize approximately 15 subjects in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle.

Study drug will be packaged in 50-g tubes from which up to 36 g of IP may be dispensed per application, i.e., the maximum dose per application. Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied (i.e., study staff will measure the 50-g tube before and after the first application to determine the fixed dose amount for each subject). If the product will be applied at home by someone other than the study subject, it is recommended that this person assist with application at the first visit to learn how the IP is applied.

Thereafter, subjects will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of IP in a tube.

Subjects enrolled in Cohort A will continue treatment for up to 12 weeks.

After the initial 15 subjects complete at least 28 days of treatment, an independent DSMB will review aggregate safety and tolerability data (including PK and electrocardiogram [ECG] data). If no safety issues are identified, additional subjects will be allowed to enroll in Cohort B (up to approximately 105 subjects). Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and similarly treated twice weekly for up to 12 weeks in the same manner as subjects in Cohort A.

All subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]), any application site reactions, adverse events (AEs), and concomitant medications used. Subjects will also be advised on permitted emollient(s) and/or sunscreen(s) use on nontreatment days during the study; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited.

At all sites with photographic capability, photographs will be taken as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional, photographic informed consent form (ICF).

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit, as indicated in the Schedule of Events (Table 2-1). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application. Subjects should not apply IP on visit days until after the visit.

In addition, a PK substudy will be conducted on Days 1 and 30 at sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 30 subjects. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for all subjects at specified time points. For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30.

Efficacy will be assessed by the number of subjects in each treatment group who achieve "success" defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA scale (i.e., 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe). In addition, efficacy criteria include assessment scales for palm/sole, scaling, roughness, fissuring, and the Dermatology Life Quality Index (DLQI), and the EQ-5D Quality of Life (QoL) Questionnaire. Ectropion Severity Scores (ESS) between the active trifarotene cream HE1 and vehicle groups will be an exploratory endpoint.

Plasma concentrations of CD5789 and its major metabolites will be measured.

Safety will be assessed by evaluating reported adverse events (AEs), changes in clinical laboratory test results, vital sign measurements, physical examinations, 12-lead ECGs, and local tolerability.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent through the post-treatment visit) will be documented.

Topical trifarotene cream HE1 was generally well tolerated in recently completed phase 3 pivotal and long-term safety studies in subjects aged 9 years and older with acne vulgaris. The local tolerability of the trifarotene cream HE1 formulation in subjects with LI is unknown and will be monitored during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) on each treated body area

(chest/abdomen, back, legs, arms, and face/neck) and will follow the procedures detailed in Section 9.4.

All subjects (Cohort A and Cohort B) who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for up to 12 weeks. During the OLE, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and Week 24 from all subjects who continue into the OLE (Table 2-2).

Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and AEs; see Section 9.4.

Figure 7-1: Double-blind Study Design

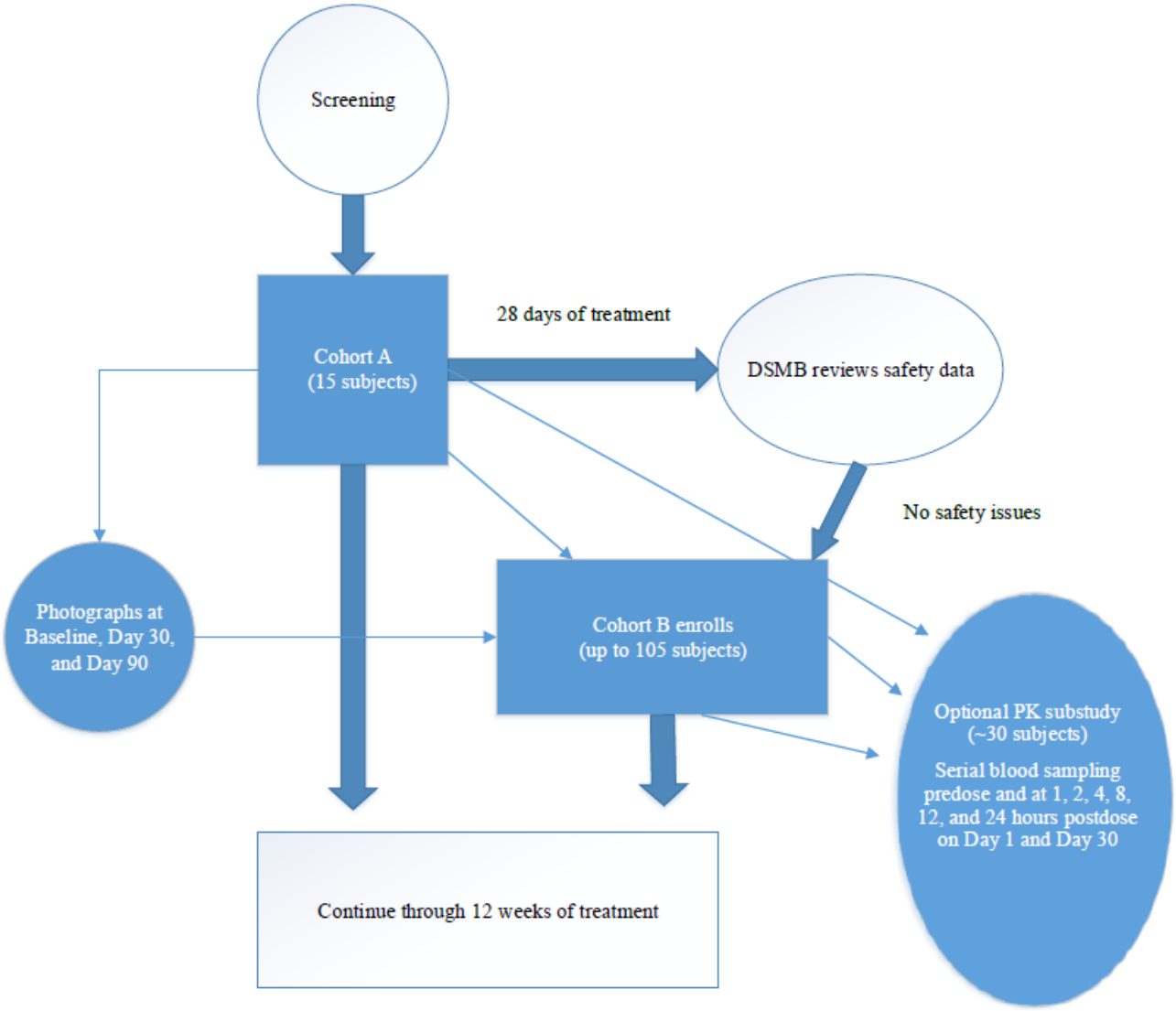
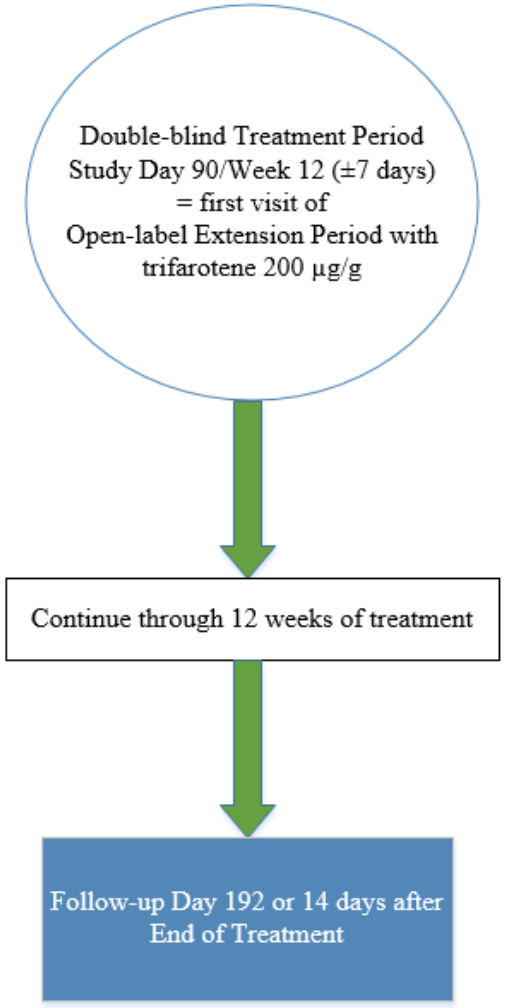


Figure 7-2: Open-label Study Design



7.2. Rationale and Discussion of Study Design

The first part of this study is a randomized, double-blind, placebo-controlled study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in subjects with LI.

In a previous proof-of-concept study (RD.03.SRE.40181E), subjects with LI applied trifarotene 50 and 100 µg/g cream to limited areas and results demonstrated a decrease in scaling with good safety and tolerance. In a phase 1 study in healthy Japanese and non-Japanese subjects (RD.03.SPR.103813), repeated topical applications of trifarotene (CD5789 cream HE1) 100 µg/g and 200 µg/g resulted in low and similar CD5789 systemic levels in all the cohorts. These studies are fully described in the current IB.

To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of 15 subjects randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly. An independent DSMB will review aggregate safety and tolerability data from the initial 15 subjects' first 28 days of treatment. If no safety issues are identified, 105 additional subjects will be allowed to enroll in Cohort B and randomized to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly in the same manner as subjects in Cohort A. All subjects in the randomized, double-blind portion of the study will be treated for up to 12 weeks and data on safety, tolerability, PK, and efficacy collected.

Subjects who successfully complete the initial 12 weeks of double-blind treatment will have the option to enter an OLE with trifarotene cream HE1 200 ug/g twice weekly for up to 12 weeks.

The OLE will collect additional safety, tolerability, PK, and efficacy data. As designed, this study will provide important information on safety, tolerability, and PK with dosing of subjects with LI for up to 6 months.

The protocol includes appropriate monitoring for safety and tolerability. If subjects develop significant local application site reactions or tolerability issues, the protocol includes language for reducing the frequency of application or halting study drug application until the symptoms abate.

7.3. Selection of Doses in the Study

Based on the results from Study RD.03.SRE.40181E and Study SRE.103813, the doses of 100 µg/g and 200 µg/g were selected for further investigation in subjects with moderate to severe LI to determine which of the 2 doses is most effective. The PoC study demonstrated efficacious treatment with 100 µg/g in adults. The PK and tolerability study showed that, when the frequency of application was reduced from daily to twice weekly, the 200 µg/g cream HE1 had good local tolerability.

Therefore, the current study will use these doses compared with vehicle, applied twice weekly on up to approximately 90% BSA in subjects with LI. The OLE will evaluate the long-term safety of the higher dose in this patient population.

7.4. Study Sites

The study will take place at approximately 40 sites in North America, Europe, Israel, and Australia.

7.5. Point of Contact

A point of contact will be identified to provide information to subjects about where to obtain information on the study, the rights of subjects, and whom to contact in case of a study-related injury. This information will be provided in the subject information and informed consent form (ICF).

7.6. End of Study Definition

A clinical trial is considered completed when the last participant's last study visit has occurred.

8. SUBJECT POPULATION

8.1. Selection of Study Population and Diagnosis

Diagnosis of LI for the purposes of this study will be a clinical diagnosis. Although some younger subjects may have had genetic testing, older subjects may not.

While LI is a rare disease and subject enrollment may be challenging, due to possible bias introduced by including household members in the same study, it is recommended that only 1 household member be included in the study to maintain the blind and ensure all assessments are independent.

8.2. Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. Subject is ≥18 years old.
2. Subject has known diagnosis of LI.
3. Subject has moderate to severe (IGA 3–4) LI on the IGA of LI severity.
4. Subject has signed an ICF at Screening before any investigational procedures.
5. Subject who is participating in optional photography has signed a photography ICF.
6. Subject who is participating in the optional PK substudy has signed a PK ICF.
7. Subject is not of childbearing potential, i.e., a female who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason, hysterectomy or bilateral oophorectomy),

   OR

- Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception:
  - bilateral tubal ligation
  - combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation
  - hormonal intrauterine device (IUD) inserted at least 1 month before Baseline

  OR

  Agrees to abstain from heterosexual intercourse during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

  AND

Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application.

8. Women of childbearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine).
9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent.
10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

8.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization, including syndromic ichthyoses.
2. Subject has current moderate or severe stinging/burning at Screening.
3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments.
4. Subject with a known lipid disorder (hypertriglyceridemia >200 mg/dL, hypercholesterolemia >250 mg/dL) unless well controlled by stable doses of lipid-lowering agents for at least 6 months.
5. Subject was previously treated with trifarotene/CD5789 in an acne or ichthyosis study.
6. Subject has any other significant concomitant disease, or poorly controlled medical condition other than LI that in the investigator's opinion may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis).
8. Subject is being treated for major depression disorder and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts.
9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening.
10. Subject with any of the following laboratory values at Screening:
    a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory
    b. Total bilirubin >1.1 mg/dL or, in case of Gilbert's syndrome, total bilirubin >3 mg/dL
    c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women
    d. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L.
11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
12. Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment.

13. Subject has a history of long QT syndrome or clinically significant ECG abnormalities, including clinically significant conduction disorders or significant arrhythmias, QTcF interval >450 ms, PR interval is not between 120 and 220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed.
14. Subject has a known allergy or sensitivity to any of the components of the investigational products.
15. Subject has been exposed to excessive UV radiations on the treated zones within 1 month before Baseline visit or is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.).
16. Subject is inherently sensitive to sunlight.
17. Subject is unable or unwilling to stop use of topical or systemic retinoids.
18. Subject is presumed to be abusing drug or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms.
19. Subject is participating in another interventional clinical trial.
20. Subject is institutionalized.
21. Subject is in any way related to the sponsor, investigator, or site personnel.

8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

8.4. Discontinuation of Study Intervention

Discontinuation from study treatment does not mean withdrawal from the study, and the remaining study procedures should be completed as indicated in the study protocol (see Section 10.2.4.5). If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

An investigator must discontinue a participant's study treatment for any of the following reasons:

- Pregnancy
- Significant study intervention noncompliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would result in a significant burden to the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for discontinuation of study treatment will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized, and receive the study intervention, and subsequently discontinue study treatment, or are withdrawn from the study will not be replaced.

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.5. Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Randomized subjects withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

9.1. Identification of Investigational Product(s)

Trifarotene cream HE1 is a cream containing 100 or 200 µg/g (0.01% [w/w] or 0.02% [w/w], respectively) of CD5789 and the following excipients: purified water, propylene glycol, allantoin, glycerin, medium-chain triglycerides, polypropylene glycol 15 stearyl ether, cyclomethicone, phenoxyethanol, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane (simulgel 600 PHA), sodium benzoate, butylated hydroxytoluene, and gluconolactone. It is an RARγ agonist characterized by its high specificity to this receptor.

Vehicle contains the same ingredients, without the CD5789.

Trifarotene cream HE1 and vehicle will be provided in cream form for topical application and will be supplied in 50-g tubes from which a maximum of 36 g of IP may be extracted.

Trifarotene cream HE1 and vehicle will be supplied by G. Production, Inc. (Galderma) in Baie-D'Urfé, QC, Canada.

9.2. Treatments Administered

For the Double-blind Treatment Period, a fixed dose (determined at Visit 2) of trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject. The IP should be applied thinly and gently rubbed in.

Study staff will apply the first administration of IP in the clinic on Day 1 after Baseline measurements, and the amount of IP used will be measured (i.e., 50-g tube will be measured before and after application to determine amount used). If the product will be applied at home by someone other than the study subject, it is recommended that this person assist with application at the first visit to learn how the IP is applied.

The maximum dose per application is 36 g (i.e., 1 tube). Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than full amount of product in a tube. Subjects will continue treatment for up to 12 weeks.

After the Day 1 visit, subjects will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Persons other than the study subject applying the study drug must wash their hands after application or use disposable vinyl gloves. In addition, a long-handled applicator will be provided for application on the back. The applicator must be washed with warm water and soap after every application.

Trifarotene cream should not come into contact with the eyes, mouth, angles of the nose, or mucous membranes. For the ectropion treatment, Q-tips are recommended for precise application on eyelids, without contact to the eye or conjunctiva. If the IP gets into the eye, it must be flushed immediately with warm water. In case of eye irritation, the subject must be seen by an ophthalmologist.

For the OLE, all subjects will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the Double-blind Period for an additional 12 weeks.

Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.

Subjects should not apply IP on visit days until after the visit, unless they are participating in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the blood draw. Among subjects participating in the PK substudy, ensure the PK line is inserted before study drug application to prevent contamination with the IP and to protect the skin around the needle insertion point from study drug application.

9.3. Selection of Timing of Dose for Each Subject

Subjects will be randomized in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply approximately the same amount of IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week at least 3 days apart on which to apply their IP (e.g., Tuesday and Friday), and maintain that regimen throughout the study. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained on the skin after the last application. Subjects should not apply the IP on visit days until after the visit, unless they participate in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the PK blood draw.

All subjects will be provided with diaries in which to record study drug application (days/times) and any areas of skin not treated (e.g., due to local reactions).

If a subject misses an IP application, they should apply the IP as soon as they remember and record the date/time in the subject diary, then wait at least 3 days and continue their regimen.

Subjects should not shower, bathe, or swim for at least 4 hours after IP application. No occlusive dressings should be used on areas to which IP is applied.

Subjects who continue into the Open-label Extension will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the Double-blind Period for an additional 12 weeks.

9.4. Dose Adjustment Criteria

Local tolerance will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability on a 0-3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) for each treated body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed:

- If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area (e.g., the face), the study drug will be applied on this area only once weekly, until the score returns to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas.
- If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., “drug holiday”). Continue to treat all other areas twice weekly provided the score is <2 on those areas.

Any changes in dosing must be documented in the subject diary and the eCRF.

9.4.1 Stopping Rules

A subject's treatment in either the Double-blind Period or the Open-label Extension must be stopped if any of the following occur:

- Subject becomes pregnant or suspects they are pregnant
- Subject has severe (score of 3) local application site AEs that do not abate with "drug holiday" and reintroduction of IP.
- Subject has clinically significant changes in laboratory values (liver function tests, cholesterol/triglycerides – which may occur with systemic retinoid use)

Any changes in dosing must be documented in the subject diary and the eCRF.

9.5. Treatment Compliance

Subjects will be asked to record their twice-weekly applications of IP in the diary during both the Double-blind Period and the OLE. Deviations from the planned doses (missed dose or timing) will be recorded on the subject's eCRF. Study personnel will review diaries at each visit and diaries will be collected as source documents. Information from subject diaries will be transcribed on the appropriate eCRF pages for documentation of subject compliance with the IP.

Study personnel will assess treatment compliance with IP regimens by weighing IP tubes before dispensing and upon return and by questioning the subject, at every postrandomization visit. A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, supplemented by tube weight. A subject who is not compliant (used 80–120% of IP tubes) will be counseled at each visit on the importance of using the IP as instructed.

Subjects who taper to once-weekly application or who take a "drug holiday" for tolerability will not be reported as having deviated from the protocol (see Section 9.4 for dose adjustment and stopping rules); any changes in dosing must be documented in the subject diary and the eCRF.

9.6. Method of Assigning Subjects to Treatment Groups

In the double-blind, parallel-group, randomized period of the study, subjects who meet study entry criteria will be randomly assigned in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. Study center will not be a blocking factor in the randomization schedule.

Premier Research will prepare the randomization schedule before the start of the study. No one involved in the study performance will have access to the randomization schedule before the official unblinding of treatment assignments. No subject will be randomized into this study more than once.

In the OLE, all subjects will receive trifarotene cream HE1 200 µg/g.

9.7. Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the Double-blind Period of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician and programmer from Premier Research who will have access to the randomization code. The statistician will have access to unblinded data if there is an unblinded DSMB review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

The investigator may discuss with the medical monitor in advance of unblinding a subject, if possible, if it is not deemed an emergency. However, the investigator has the ultimate decision for unblinding a subject for medical treatment and no procedures will prevent or delay necessary unblinding in an emergency for the subject's safety. For emergency unblinding, study personnel will use the IWRS code. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

The primary analysis period is the first 12 weeks of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after database lock has been achieved. A second analysis will take place for endpoints assessed from Week 12 through the OLE.

9.8. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods (Table 9-1), as applicable. Washout may be up to 3 months, as necessary.

Table 9-1: Washout Periods for Prohibited Medications

Medication	Washout Period
Topical Treatments	
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	2 weeks
Systemic treatments	
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines (except Vitamin D analogues taken at stable dose since at least 1 month)	8 weeks
QT prolonging drugs	5 half lives
Enzymatic inductors (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (not all inclusive: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives
Monoclonal antibodies (e.g., anti-IL17)	5 half lives

During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower, but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.

After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.

9.8.1 Permitted Therapies

Subjects will be advised on permitted emollient(s) for use as often as needed on nontreatment days during the study; on treatment days, the use of emollient(s) is permitted except within 4 hours before or after study drug application. Similarly, protective sunscreen should be applied as often as needed, except within 4 hours before or after study drug application. Subjects may use their standard of care treatment on their faces and/or palms/soles after the Week 4 assessment if they experience a worsening of IGA in those areas. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. These standard of care treatments should be approved by the investigator and documented in the eCRF.

Subjects who enter the OLE must stop standard of care treatment. If they experience a worsening of IGA they may use standard of care treatment on their faces and/or palms/soles after the Week 16

visit if the standard of care does not contain prohibited medications. If those standard of care treatments include prohibited medications, the subject should be discontinued from the study.

Other concomitant medications are allowed (e.g., analgesics, antihistamines), but should be limited to those medications considered necessary. All concomitant medications, both prescribed and over-the-counter, should be recorded in the eCRF.

9.8.2 Prohibited Therapies

The medications listed in Table 9-1 are prohibited during the study. Balneotherapy is also prohibited during the Screening Period and during the study.

Subjects may not use concomitant keratolytics such as urea, salicylic acid, alpha, or beta hydroxyacids. Subjects may not use topical or systemic retinoids. Subjects may not take more than 3500 IU/day Vitamin A (e.g., as in a multivitamin). Use of benzoyl peroxide is permitted on nontreatment days for subjects with concomitant acne only); it must not be applied on treatment days due to risk of inactivation of trifarotene by benzoyl peroxide.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continued treatment in the study, at the investigator's discretion with consultation with Mayne Pharma LLC and the medical monitor. For enrolled subjects who require prescription of a systemic azole, the principal investigator should discuss with the medical monitor whether the subject may continue in the study.

9.8.3 Restrictions

Subjects should not shower, bathe, or swim for at least 4 hours after study drug application. No occlusive dressings should be applied to areas where study drug was applied.

Subjects should only use investigator-approved emollients, and should not use them on treatment days within at least 4 hours before and after study drug application.

In addition, subjects should take protective measures to avoid exposure of treated areas to sunlight, such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet), and/or seeking shade or shelter from the sun.

9.9. Treatment after End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.10. Dispensing and Storage

The test product supplied by Mayne Pharma LLC is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Premier Research. Until the IP is dispensed to the subjects, it must be stored at 20–25°C (68–77°F), with excursions permitted to 15–30°C (59–86°F); do not freeze and with the tube kept tightly closed in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

9.11. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of subjects (subject number) who received the IP. The investigator will not supply the IP to any person except those named as subinvestigators on the Form Food and Drug Administration (FDA) 1572, designated study personnel, and subjects in this study. The investigator will not dispense the IP from any study sites other than those listed on the Form FDA 1572. Investigational product(s) may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Each subject will be given enough tubes of study drug to apply up to 1 tube-full (approximately 36 g of clinical trial material) per treatment day until the next study visit. Tubes will be packed 2 to a carton, and each subject will receive enough cartons to have the maximum number of tubes needed until the next study visit. The number of study drug tubes the subject needs to provide enough IP until the next visit is shown in Table 9-2.

Table 9-2: Amount of Study Drug Needed Per Visit

Treatment Period	Number of Cartons	Number of Tubes
Double-blind Treatment Period		
Baseline	3	6
Day 14	4	8
Day 30	6	12
Day 60	6	12
OLE		
Day 90	3	6
Day 104	4	8
Day 120	6	12
Day 150	6	12

Each carton will be weighed before dispensing and subjects are to bring all cartons and tubes back at each study visit, whereupon study staff will weigh them again to estimate study drug use and compliance.

Upon completion of the study, the IP (partly used, unused, and empty tubes) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.12. Labeling and Packaging

Labeling and packaging of IP will be performed by Catalent Pharma Solutions, Philadelphia, PA, USA.

Tubes will be packaged in cartons comprising 2 tubes each. Tubes will be labeled with inner and outer booklet labels, and carton number. Each carton will also be labeled with inner and outer booklet labels and numbered.

9.12.1 Labeling

The tubes will have a label affixed that meets the applicable regulatory requirements and may include, but is not limited to, the following: subject identifier, IP name, lot number, protocol number, carton number, caution statement, storage, and sponsor identification.

Save all empty packaging or packaging containing unused tubes for final disposition by the sponsor or contract pharmacy.

Final labeling will comply with the regulatory requirements of each country where the study will be conducted.

9.12.2 Packaging

Investigational products will be packaged in high-density polyethylene, 35×100 mm tubes weighing 50 g from which a maximum of 36 g of IP can be extracted. Trifarotene cream HE1 and vehicle will be packaged so as to be blinded to the investigator, the study clinic personnel, and the subjects.

10. STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

Subjects who agree to participate in the photography and/or PK substudies must provide written informed consent before photographs or serial blood samples are collected.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

10.1.1 Overall Study Schedule

The overall study duration is expected to be approximately 19 months.

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening: up to 35 days (after signing informed consent, if necessary, washout may be up to 3 months, and subjects should return to the site after washout to complete the study eligibility requirements).
2. Double-blind treatment: Twice weekly for 12 weeks.
3. Optional Open-label Extension treatment: Twice weekly for 12 weeks.
4. Follow-up: 14 days after last study drug application.

The maximum treatment duration for each subject is approximately 12 weeks for subjects who choose not to continue into the OLE, and 24 weeks for those who choose to continue.

The maximum study duration for each subject is approximately 229 days (33 weeks).

10.2. Study Periods and Visits

It is suggested that quality of life assessments be conducted first to avoid any bias, and that the IGA be recorded as the first LI assessment at every visit.

10.2.1 Screening and Washout

10.2.1.1 Screening Visit (Visit 1)

The subject must complete eligibility screening within 35 days before randomization in the study. The following procedures will be performed during Screening:

1. Obtain written informed consent.
2. Assign a screening number when a subject begins screening.
3. Assess inclusion/exclusion criteria.
4. Collect demographic information.

5. Record medical history, including current therapies (e.g., prescription and nonprescription medications).
6. Perform a physical examination.
7. Measure vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse).
8. Measure height, weight, and calculate body mass index (BMI).
9. Record IGA.
10. Record VIIS.
11. Record roughness assessment.
12. Record palm/sole assessment.
13. Record palm/sole assessment of fissuring.
14. Record ectropion score.
15. Perform a 12-lead ECG.
16. Collect blood and urine for laboratory tests.
17. Perform serum pregnancy test for WOCBP.

Procedures for rescreening subjects who initially fail to meet study entry criteria are described in Section 14.3.

10.2.1.2 Washout

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout the prohibited topical and systemic treatments with designated washout periods, as applicable (Table 9-1). Washout may be up to 3 months, as necessary.

During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.

After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements (Section 10.2.1.1).

10.2.2 Double-blind Treatment Period

Eligible subjects who have washed out prohibited medications will be randomized to double-blind study drug.

10.2.2.1 Baseline Visit (Visit 2, Day 1)

The following procedures will be performed on Day 1 in the study clinic:

1. Review inclusion/exclusion criteria.
2. Record responses to DLQI and EQ-5D Quality of Life Questionnaires

3. Perform physical examination.
4. Record vital signs (blood pressure and pulse).
5. Record concomitant medications and concomitant therapies.
6. Record IGA.
7. Record VIIS.
8. Record roughness assessment.
9. Record palm/sole assessment.
10. Record palm/sole assessment of fissuring.
11. Record ectropion score.
12. At sites where the photographic substudy is conducted, take photographs of subjects who have provided informed consent for the photography.
13. Perform a 12-lead ECG.
14. Perform urine pregnancy test for WOCBP.
15. Collect blood and urine for routine laboratory tests (subject must be fasting; i.e., at least 8 hours).
16. Randomize via IWRS.
17. Collect a predose PK blood sample (all subjects).
18. Among subjects who consent to participate in the PK substudy, ensure that PK lines are placed before IP application. The IP will be applied in the clinic at this visit, and samples for PK will be taken at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1.
19. Among subjects in the PK study, perform additional ECGs at times of serial sampling.
20. Clinic staff instructs subject on study drug application, applies initial study drug dose and measures amount used (i.e., study staff will weigh the 50-g tube before and after the first application to determine the fixed dose amount for each subject). If the product will be applied at home by someone other than the study subject, it is recommended that this person assist with application at this visit to learn how the IP is applied.
21. Assess and record local tolerance/AEs.
22. Dispense study drug and diaries.
23. Advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that at least 24 hours must have elapsed since IP application before their next visit. Subjects should not to apply IP on visit days until after the visit.

10.2.2.2 Telephone Visit (Day 7)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited), and remind subjects that at least 24 hours must have elapsed since IP application before their next visit. Subjects should not apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.2.3 Visit 3 (Day 14 ±5 days)

The following procedures will be performed on Day 14 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Record IGA.
5. Record VIIS~~IGA~~.
6. Record roughness assessment.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring
9. Record ectropion score.
10. Assess local tolerance.
11. Record AEs and review diary.
12. Collect a PK blood sample (all subjects).
13. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
14. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.
15. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.

10.2.2.4 Visit 4 (Day 30 ±7 days)

The following procedures will be performed on Day 30 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.

2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Record IGA.
5. Record VIIS.
6. Record roughness assessment.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring
9. Record ectropion score.
10. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
11. Assess local tolerance.
12. Record AEs and review diary.
16. Perform a 12-lead ECG
17. Perform a urine pregnancy test for WOCBP.
18. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
19. Collect a PK blood sample (all subjects).
20. Among subjects who consent to participate in the PK substudy, ensure that PK lines are placed before IP application. The IP will be applied in the clinic at this visit, and samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose.
21. Among subjects in the PK study, perform an additional ECGs at times of serial sampling.
22. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
23. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before and after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.
24. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
25. Provide information about OLE option to study subject.

10.2.2.5 Telephone Visit (Day 45)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited), and remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary. Staff will remind subject about OLE option.

10.2.2.6 Visit 5 (Day 60 ±7 days)

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Perform a urine pregnancy test for WOCBP.
5. Record IGA.
6. Record VIIS.
7. Record roughness assessment.
8. Record palm/sole assessment.
9. Record palm/sole assessment of fissuring
10. Record ectropion score.
11. Assess local tolerance.
12. Record AEs and review diary.
13. Collect a PK blood sample (all subjects).
14. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
15. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before and after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.
17. Provide information about OLE option.

10.2.2.7 Visit 6 (90 ±7 days) or Early Termination

The following procedures will be performed on Day 90 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
2. Perform a physical examination.
3. Record vital signs (blood pressure and pulse).
4. Record concomitant medications and concomitant therapies.
5. Record IGA.
6. Record VIIS.
7. Record roughness assessment.
8. Record palm/sole assessment.
9. Record palm/sole assessment of fissuring.
10. Record ectropion score.
11. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
12. Assess local tolerance.
13. Record AEs and review diary.
14. Perform a 12-lead ECG.
15. Perform a urine pregnancy test for WOCBP.
16. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
17. Collect a PK blood sample (all subjects).
18. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.

For subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 12 weeks of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing, PK from Day 90/Week 12 will be carried over to the OLE and will not be repeated. Subjects will have up to 7 days to decide to enter the OLE; if the subject chooses to continue into OLE, the following additional procedures will be done:

1. Have the subject sign OLE-specific informed consent.
2. Measure subject's weight.
3. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that at least 24 hours must have elapsed since IP application before the

PK draws at the Week 16 and Week 24 Visits, and not to apply IP on visit days until after the visits.

4. Weigh new study drug tubes and dispense enough additional study drug until next visit (only for subjects who choose to continue into the OLE).
5. Dispense study diary.

10.2.3 Follow-up Telephone Call (±14 days after Day 90) – Only Subjects Who Do Not Continue into Open-label Extension

Clinic staff will telephone subjects who choose not to continue into the Open-label Extension within 14 days after Day 90 to assess any ongoing AEs.

10.2.4 Open-label Extension

Subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 12 weeks of double-blind treatment may choose to continue into an optional 12-week OLE with trifarotene cream HE1 200 µg/g. During the OLE, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and 24 from all subjects who continue into the OLE.

10.2.4.1 Telephone Visit (Day 97)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.2 Visit 7 (Week 14; Day 104 ±5 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.

11. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
12. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.at the Week 16 and Week 24 Visits, and not to apply IP on visit days until after the visit.

10.2.4.3 Visit 8 (Week 16; Day 120 ±7 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Perform a 12-lead ECG.
11. Perform a urine pregnancy test for WOCBP.
12. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
13. Collect a PK blood sample (all subjects)
14. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
15. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.

10.2.4.4 Telephone Visit (Day 134)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days (use of

emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.5 Visit 9 (Week 20; Day 150 ±7 days)

The following procedures will be performed at each study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Perform a urine pregnancy test for WOCBP.
11. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
12. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.

10.2.4.6 Visit 10 (Week 24; Day 180 ±7 days) or Early Termination

The following procedures will be performed at Week 24 in the study clinic:

1. Perform a physical examination.
2. Record vital signs (blood pressure and pulse).
3. Record concomitant medications and concomitant therapies.
4. Record IGA.
5. Record VIIS.
6. Assess roughness.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring.
9. Record ectropion score.
10. Assess local tolerance
11. Record AEs and review diary.

12. Perform a 12-lead ECG.
13. Perform a urine pregnancy test for WOCBP.
14. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
15. Collect a PK blood sample (all subjects)
16. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.

10.2.4.7 Follow-up Evaluation – Open-Label Extension (Week 26/Visit 11)

At 14 days after the last administration of the IP, the following procedures will be performed:

1. Perform a physical examination.
2. Record vital signs (blood pressure and pulse).
3. Record any concomitant medications/therapies.
4. Record IGA.
5. Record VIIS.
6. Assess roughness.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring.
9. Record ectropion score.
10. Assess and record AEs occurring since the last evaluation and review diary.
11. Perform a urine pregnancy test for WOCBP.

10.3. Assessments

The 5-point IGA is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. The IGA scale was developed with the support of experts from academic reference centers for the treatment of ichthyosis. Each level of severity will consider both the severity of scaling and the severity of roughness (Section 10.3.1.2). While retinoid treatment is expected to reduce scale, it may increase erythema; therefore, in this study, erythema will be evaluated as part of local tolerability.

10.3.1 Efficacy Variables

All efficacy measurements will use scales previously used for dermatological studies or as defined in the following sections.

10.3.1.1 Investigator's Global Assessment

The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear and at least a 2-grade change from Baseline at Week 12/EOT in the Double-blind Period on a 5-point IGA full body scale.

The investigator will rate the subject's condition using the 5-point IGA at each time point shown in the Schedule of Events (Section 2.2).

The IGA will be measured on a 5-point scale, excluding the following areas: knees, elbows, neck, palms, soles, axillae, groin, and scalp:

0	Clear	No scaling and no roughness
1	Almost Clear	Occasional fine scales; hardly palpable roughness (mostly smooth)
2	Mild	Small and fine scales predominate; no more than a few large scales; mild roughness on palpation
3	Moderate	Some large scales that may be thick; coarse roughness on palpation
4	Severe	Confluent, primarily large (>1 cm), thick scales with plate-like hyperkeratosis

10.3.1.2 Visual Index for Ichthyosis Severity – Scaling

The secondary endpoint is the number of subjects in each treatment group who experience a severity score of 0 or 1 at Week 12/EOT on the overall 16-point VIIS for scaling.

The investigator will rate the subject's condition using the 5-point VIIS for each body area (chest/abdomen, back, legs, and arms) and an overall score at each time point shown in the Schedule of Events (Section 2.2):

0	Normal skin; no perceptible scale or smoothening
1	Areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings, shininess, waxiness) or small scales (visibly separated/fractured stratum corneum)
2	Confluent smoothening (diminished fine skin markings, shininess, waxiness) or small scales (visibly separated/fractured stratum corneum)
3	Confluent scales (visibly separated/fractured stratum corneum) including some large (>1 cm), thick scales
4	Confluent, primarily large, thick scales

10.3.1.3 Individual Score for Roughness

The amount of roughness of the skin overall will be measured on a 5-point scale.

0	Clear	Smooth skin
1	Almost Clear	Hardly palpable roughness
2	Mild	Mild roughness (fine sand paper-like)
3	Moderate	Moderate, coarse roughness (coarse sand paper-like)

4	Severe	Very coarse skin (broken cornflakes-like)

10.3.1.4 Palm/Sole Assessment

Thickening of the skin on the palms and soles will be measured on a 5-point scale.

0	Clear	No thickening, no roughness, no fissure
1	Almost Clear	Only slight thickening, minimal to no roughness, no fissures
2	Mild	Some thickening, mild roughness on palpation, few fissures may be present
3	Moderate	Substantial and diffuse thickening, coarse roughness on palpation may be present, fissures may be present
4	Severe	Very thickened and rough skin, numerous fissures

10.3.1.5 Palm/Sole Fissuring Assessment

Fissuring will be assessed by recording the presence or absence of fissures, the number of fissures present, and the pain associated with each fissure. A fissure is a longitudinal and deep crack that separates the stratum corneum and may penetrate down to the dermis, causing pain and sometimes bleeding. The subject will assess pain associated with fissures as ranging from 0-3 (none, mild, moderate, severe).

10.3.1.6 Dermatology Life Quality Index

The DLQI is a dermatology-specific Quality of Life instrument. It is a simple 10-question validated questionnaire with 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment); higher scores indicate poorer quality of life. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology.

10.3.1.7 EQ-5D Quality of Life Questionnaire

The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the subject's self-rated health on a vertical 0-100 VAS. This can be used as a quantitative measure of health outcome that reflects the subject's own judgment.

10.3.1.8 Ectropion Severity Score

The Ectropion Severity Score (ESS), has a maximum score of 8 points. A higher score indicates a worse ectropion. The score takes the severity of ectropion in terms of lateral and medial apposition, scleral show, conjunctival show, and roundness of the eye into account and gives an indication of

the functional aspects involved in ectropion by scoring redness, excess tear film, and the position of the lacrimal punctum.[14]

	Points per Item		
	0	0.5	1
Lateral apposition	Nonaffected	—	Affected
Medial apposition	Nonaffected	—	Affected
Sceral show	No	≤1 mm	>1 mm
Conjunctival show	No	—	Yes
Excess tear film	No	—	Yes
Redness of the eye	No	—	Yes
Round canthus	No	—	Yes
Punctum lacrimale	Invisible	Emerging	Visible
Maximum score			8 points

Figure 10-1: Ectropion Severity Score

Source: Korteweg SFS, Stenekes MW, van Zyl FE, Werker PMN. Paralytic Ectropion treatment with lateral periosteal flap canthoplasty and introduction of the ectropion severity score. *Plast Reconstr Surg Glob Open.* 2014;2(5):e151.

10.3.1.9 Photography Substudy

All sites that have photographic capability will take photographs as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional photographic informed consent form (ICF).

10.3.2 Clinical Pharmacology

10.3.2.1 Pharmacokinetic Analysis Methods

The pharmacokinetic characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis (NCA).

10.3.2.2 Pharmacokinetic Parameters

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit for trough values.

Subjects who provide written informed consent to participate in the optional PK substudy will provide blood samples for PK analysis predose on Day 1 and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30.

The PK parameter estimates will be completed using WinNonlin (Pharsight Corporation) software using the actual elapsed times from dose administration to sample collection (i.e., not nominal time).

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the maximum concentration (C_{max}) and the time of C_{max} (T_{max}). Additional details of the parameters and their calculation and evaluation will be included in the statistical analysis plan (SAP).

Table 10-1 shows the PK parameters that will be computed for each subject for samples obtained over the planned sampling intervals.

Table 10-1: Pharmacokinetic Parameters

Parameter	Description of Parameter
C_{max}	Maximum (or peak) serum concentration
T_{max}	Time at which C_{max} is observed
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration
$AUC_{(0-inf)}$	Area under the plasma concentration-time curve from time 0 to infinity (if data permit)
$t_{1/2}$	Apparent first order terminal elimination half-life
λ_z	Apparent terminal phase rate constant (if data permit)

10.3.3 Sample Collection

Samples will be collected at the time points specified in the Schedule of Events (Section 2.2). Specimen preparation, handling, shipment, and storage for the complete blood count, chemistry, and urinalysis are described in the study laboratory manual. Finding veins in subjects with this disease can be challenging. Blood draws will be done at the corresponding study visits before application of the IP and should be 24 hours after IP application. Subjects must not apply the IP to the area where blood will be drawn within 24 hours before their next study visit to avoid contamination of the blood by IP that remained in the skin. For subjects in the PK substudy, a cannula should be placed before IP application and the cannula site may be occluded to prevent contamination with IP.

Actual PK sample times for subjects in the PK substudy will be recorded in the eCRF.

Blood

For subjects not in PK substudy:

The expected amount of blood to be drawn at each visit varies from approximately 6 mL to a maximum of 21 mL (Screening Visit only). The total amount of blood drawn for the study will be about 123 mL per subject, unless the subject takes part in the PK substudy.

For subjects in PK substudy:

For subjects who opt to participate in the PK substudy, extra blood samples will be drawn at Visit 2 and at Visit 4 for PK analysis. The amount of blood to be drawn per subject at each of these visits

will be approximately 54 mL. For subjects taking part in the substudy, the total amount of blood drawn for the entire study will be approximately 195 mL.

Urine

Urinalysis will be performed at central laboratory. Dipstick and urine pregnancy tests will be conducted on site.

10.3.4 Safety Variables

Safety assessments will include the evaluation of AEs, including local tolerability (stinging/burning, pruritus, and erythema), clinical laboratory assessments, vital signs, 12-lead ECGs, and physical examinations.

10.3.4.1 Clinical Laboratory Safety Assessments

10.3.4.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 2.2).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides
Coagulation Panel:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones
Pregnancy Test:	for women of childbearing potential only; serum at Screening, urine at each other visit.
Serology	Hepatitis B surface antigen, and hepatitis C

All blood samples for the clinical laboratory tests must be taken in a fasting state, at least 8 hours after the previous drug application.

Blood and urine samples for hematology, and serum chemistry will be sent to a central laboratory for analysis. Urine pregnancy tests and dipstick will be conducted at the study sites.

10.3.4.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in

both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

Samples for assessment of clinical laboratory tests will be transported to the Clinical Reference Laboratory (see the study laboratory manual for addresses).

10.3.4.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Mayne Pharma LLC prior to beginning the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically significant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical significance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically significant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.4.2 Clinical Examinations

10.3.4.2.1 Vital Signs

Vital signs, including height and weight (only assessed at Screening), blood pressure, and pulse will be measured.

10.3.4.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. All ECG recordings will be identified with the subject number, date, and time of the recording. Gel ECG electrodes may be used for ECGs because they are more conductive and cause less trauma on compromised skin. Efficacy assessments should be conducted before ECGs to avoid possible artefact/changes from the ECG.

For subjects in the PK substudy, additional ECGs will be performed postdose during serial blood sampling on Day 1 and Day 30.

If there is a marked prolongation of the QT/QTc interval during treatment, a subject should be discontinued from the IP but remain in the study until full resolution of the event. The DSMB will be informed immediately of such an occurrence.

10.3.4.2.3 Physical Examination

A complete physical examination excluding the genitourinary examination will be performed at Screening, while limited physical examinations (to include HEENT, cardiorespiratory, abdomen, and range of motion) will be performed as indicated in the Schedule of Events (Section 2.2).

10.3.4.2.4 Other Safety Variables

Local tolerability will be assessed on a 0-3 scale (none, mild, moderate, severe). All application site reactions will be recorded as TEAEs in the diary. These should include the date and severity of the TEAE.

10.3.4.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in subjects treated with control product are also considered AEs.

11.1.2 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADRs).

The phrase “responses to an investigational product” means that a causal relationship between an investigational product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IP qualify as ADRs.

All AEs for which the judgment of relationship to IP is “possible” or higher will be considered ADRs. If a relationship to IP is not provided, then the AE must be treated as if it were “possible.”

11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For a preapproval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events.

11.1.4 Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first application of IP (trifarotene or vehicle) and not more than 14 days after the last application of IP.

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review by a study monitor.

All reported AEs, including local and systemic AEs not meeting the criteria for SAEs, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All reported AEs occurring while on study must be documented appropriately regardless of relationship. All reported AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of a reported AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study clinic personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 14 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs. In addition, although local tolerability will be assessed on a 0-3 scale, all application site reactions should be recorded as AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as follows:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3 Action(s) Taken

All AEs will be treated/managed according to standard practice. The following actions may be taken with regard to the IP. Section 9.4 describes dose adjustment and stopping rules for individual subjects.

Action(s) taken may consist of the following:

Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome of an AE at the time of last observation will be classified as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to IP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related	An AE with a reasonable time sequence to administration of the IP, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Related	An AE occurring in a causal plausible time relationship to IP administration that cannot be attributed to a concurrent disease or other drugs, chemicals, or events. The AE relationship to the IP must be assessed separately by the investigator and Mayne Pharma LLC.

11.2.3 Documentation

Any AE that occurs during the Screening Period will be captured as on the AE page of the eCRF (not medical history). All AEs that occur within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP(s)

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject may be withdrawn for treatment but continue to be followed for efficacy and safety in the study. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

It is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

Any AE will be followed (up to a maximum of 14 days after the last dose of IP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to Premier Research within 24 hours of first becoming aware of the event by e.g., completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the Premier Research by one of the following methods:

Email: globalPV-US@premier-research.com

Email: PVDS-ROW@premier-research.com

Fax number: +1 215 972 8765

Fax number: +421 2 6820 3713

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of IP(s)
- Date of last dose of IP(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s) ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, adverse event, date of occurrence, subject identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the Premier Research Pharmacovigilance Department using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB)/independent ethics committee (IEC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.2 Adverse Drug Reactions

All ADRs should be reported by the investigator in the eCRF.

Suspected serious ADRs must be reported to the sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.3 Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported by Premier Research to Mayne Pharma LLC in aggregate monthly status reports.

11.3. Special Considerations

11.3.1 Adverse Events of Special Interest

Since topical retinoids are associated with local application site AEs, particularly when beginning treatment, these events will be followed closely during the study and considered AEs of special interest (AESIs).

11.3.2 Pregnancy

All WOCBP who participate in the study should be counseled on the need to practice highly effective birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during IP treatment will be immediately discontinued from study treatment. The investigator must report the pregnancy of any woman who becomes pregnant during or within 30 days after discontinuing treatment as if it were an SAE within 24 hours of learning of the pregnancy, to Premier Research Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The

investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an SAE and AE form (entering the event temporarily as nonserious on both forms) provided by the sponsor or its designee. If a partner of a male study subject becomes pregnant, the investigator must report the pregnancy as soon as possible after learning of it to the Premier Research Pharmacovigilance using the Pregnancy Data Collection Form. A separate pregnant partner ICF will be required.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy in a study subject. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

Among the clinical studies, 12 pregnancies were reported: 4 resulted in normal births; 5 resulted in spontaneous abortions (none of which was considered related to CD5789); 1 was electively aborted, and 2 were lost to follow-up (IB for CD5789 Cutaneous Formulation).

12. DATA SAFETY MONITORING BOARD

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including LI. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate under a charter that will be finalized prior to the start of the study. The DSMB will meet at least 3 times during the conduct of the study: when the study begins, when 15 subjects have enrolled in Cohort A and have completed at least 28 days of treatment, and after 60 subjects have enrolled in the study.

The DSMB will meet after 15 subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data (including PK and ECG results). The safety data will be unblinded. At that time, the DSMB will decide whether Cohort B may begin enrolling. The DSMB will have the authority to recommend to the sponsor that the study be modified, placed on hold, or stopped if serious safety issues are discovered. The DSMB will provide its input to Mayne Pharma LLC. Any protocol changes the DSMB may suggest will be submitted to all applicable regulatory bodies for review and approval.

In case of significant toxicity, the DSMB may choose to review the available safety data and recommend stopping recruitment in a particular dose group.

Stopping rules for individual subjects are in Section 9.4.1.

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. A SAP that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a P value of ≤ 0.05 will be considered statistically significant.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will include the number and percentage of subjects in each category.

The primary analysis period is the first 12 weeks of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after the database is locked. A second analysis will take place for endpoints assessed from Week 12 through the OLE Period. The baseline for the safety and efficacy parameters will be measured at Visit 1 or Visit 2, per the Schedule of Events for both the Double-blind Period (Table 2-1) and OLE (Table 2-2).

13.1.1 Analysis Populations

The following 5 analysis populations are planned for the Double-blind Period of this study:

- Safety: all subjects who are randomized to treatment and receive at least 1 application of study drug in the Double-blind Period. This population will be the primary population for analyses of safety.
- Intent-to-treat (ITT): all randomized subjects. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study.
- Modified intent-to-treat (mITT): all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period.
- Per-protocol (PP): subjects in the mITT Population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations.
- Pharmacokinetic: all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. This population will be used to summarize all PK endpoints.

The following analysis populations are planned for the OLE of this study:

- OLE Safety: all subjects who complete the 12-week Double-blind Treatment Period and receive at least 1 application of study drug in the OLE.
- OLE ITT: all subjects who complete the 12-week Double-blind Treatment Period and sign the OLE informed consent.
- OLE mITT: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6.

- OLE PP: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study.

Inclusion in the analysis populations will be determined prior to database lock.

If a subject is randomized incorrectly or is administered the incorrect IP, analyses of the ITT and mITT populations will be based on the assigned treatment whereas all other analyses will be based on the actual treatment received.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

For the Double-blind Period, the numbers of subjects randomized, completing Week 12 of the study, and withdrawing early from the Double-blind Period, along with reasons for withdrawal, will be tabulated overall and by randomized treatment group. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated by randomized treatment group. This analysis will be conducted for the ITT population.

For the OLE, the number of subjects entering the OLE, completing the study, and withdrawing early, along with reasons for withdrawal, will be tabulated overall. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated. This analysis will be conducted for the OLE ITT population.

13.1.2.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations promptly. All deviations must be addressed in study source documents, and reported to Premier Research or Mayne Pharma LLC. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

Subjects who taper to once-weekly application or who take a “drug holiday” will not be reported as having deviated from the protocol.

13.1.2.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for the ITT and OLE ITT populations.

Demographic variables will include age, sex, race, ethnicity, height, weight, and BMI. Baseline subject characteristics will include medical history, physical examination findings, and IGA score.

Prior and concomitant medications will be summarized by randomized treatment group, by the number and percentage of subjects taking each medication, and classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of each subject's dose, and in terms of duration of exposure for each period. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group. Additionally, the number of subjects who are compliant with investigational product will be presented by treatment group for the Double-blind Period and overall for the OLE.

Subjects who taper to once-weekly application or who take a "drug holiday" will not be reported as having deviated from the protocol.

13.1.4 Efficacy Analysis

The ITT population will be used as the primary population for the primary analysis of efficacy at Week 12. Select efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE using the OLE ITT, OLE mITT, and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE.

13.1.4.1 Efficacy Endpoints

Primary efficacy endpoint: The proportion of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 2-grade change from Baseline at Week 12/EOT in the Double-blind Period on the 5-point IGA scale.

Secondary: The secondary endpoints are as follow:

- The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Week 12:
  - 5-point VIIS scale for scaling from Baseline through Week 12
  - Individual score for roughness (Scale: 0–4) overall
  - Palm/sole Assessment (Scale: 0–4)
  - Quality of life per DLQI
- The difference in proportion of subjects with presence of fissures on palm/soles (presence/absence, number of fissures, and pain associated with fissures [on a 0-3 scale]) at Week 12 between the active trifarotene cream HE1 and vehicle groups

Exploratory: The exploratory endpoints are as follow:

- The difference in mean ectropion scores (ESS of 0–8) between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12
- The difference in quality of life per EQ-5D-5L scores between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12

13.1.4.2 Primary Analysis

For the Double-blind Period only, the number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT will be presented. The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group, 95% CIs for the differences, and P-values for the differences in treatment will also be presented.

Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from baseline will be provided for IGA scores for both periods.

13.1.4.3 Secondary Analyses

Secondary and exploratory efficacy endpoints will be analyzed separately for each period (Double-blind and OLE) using descriptive statistics.

Additionally, for the Double-blind Period only, change from Baseline in continuous secondary endpoints through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate.

For subjects who report having fissures, descriptive summaries of the number of fissures and pain related to fissures will also be presented by treatment group and body area for each period.

The DLQI scores will also be analyzed using descriptive statistics through Week 12.

The proportion of subjects with at least a 50% reduction in IGA score from Baseline will be analyzed using the same logistic regression analysis described in Section 13.1.4.2.

13.1.4.4 Exploratory Analyses

Descriptive summaries and the changes from will be provided for ectropion scores and EQ-5D-5L scores by visit for each period. No formal inferential analyses will be conducted for exploratory endpoints.

13.1.4.5 Corroborative, Sensitivity, and Other Analyses

To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using multiple imputation (MI) for the Double-blind Period only. Multiple-imputations will be used to replace missing IGA outcomes using multiple draws from the posterior predictive

distribution estimated from the treatment groups. IGA scores will be imputed and then categorized as treatment success according to Section 13.1.4.1. Imputation will not be performed for the OLE. Full details will be specified in the SAP.

The proportion of subjects who experience a 2-grade change from baseline to Week 12 in individual score for roughness and palm/sole assessment will also be explored using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group and the 95% CIs for the differences will be presented.

For analyses involving study site, if the number of subjects per site is small, sites may be pooled for safety and efficacy analysis or omitted from statistical models as the anticipated number of subjects per site is small, treatment is self-administered, and the sites are using standardized procedures for all assessments. If the distribution of enrollments at sites is such that one or few are enrolling a majority of subjects, a subgroup analysis by site may be performed. The final determination will be made prior to database lock.

Details of these analyses will be further detailed in the SAP.

13.1.5 Clinical Pharmacology Analyses

13.1.5.1 Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics. Descriptive statistics reported will include the arithmetic mean, SD, CV%, geometric mean, minimum, maximum, and median. Only the range and the median will be reported for T_{max}, as this is a categorical parameter. The PK parameters will also be summarized by treatment using descriptive statistics.

Individual plasma concentration plots and mean data graphs will be produced using both linear and semi-logarithmic scales. Mean data graphs will show plasma concentration profiles by treatment group.

Pharmacokinetic plasma parameter estimates and summaries will be completed for the subjects in the PK population. Testing of PK parameters will be outlined in the SAP.

13.1.6 Safety and Tolerability Analyses

Safety analyses through Week 12 of the Double-blind Period will be conducted using data from the Safety Population and safety analyses in the OLE will be conducted using the OLE Safety Population (as defined in Section 13.1.1). Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, and physical examination results. No formal inferential analyses will be conducted for safety variables in either period.

13.1.6.1 Local Tolerability

During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for each treated body area (chest/abdomen, back, arms, legs, and face/neck). Descriptive summaries will be presented by period, treatment group, and visit.

13.1.6.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1 or higher.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first, or
- AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first.

The number and percentage of subjects with AEs will be displayed by each treatment group in the Double-blind Period and overall in the OLE by system organ class and preferred term. Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.6.3 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each treatment group at each time point in each period.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory parameter by treatment group and by study visit in each period.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.1.6.4 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse for each period.

The number of subjects with vital signs values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each parameter by period, by treatment group and by study visit. Pre- and post-treatment values may also be presented with an analysis of mean changes from baseline.

13.1.6.5 Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point in each period. Abnormal results will be grouped as clinically significant and not clinically significant.

A comparison of QT results will be presented. Summary statistics will be displayed by period, by treatment group, and by visit for QT and the QT interval corrected for heart rate (QTc) calculated using Fridericia's QT correction methods.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTcF interval (Fredericia's correction methods), and HR for each treatment group at each time point in each period.

13.1.6.6 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group in each period.

13.1.7 Interim Analysis

No interim analyses are planned.

13.2. Sample Size Determination

Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively. This study is not powered to detect a difference between the 2 active arms.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Mayne Pharma LLC agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with ICH GCP, and the applicable United States (US) Code of Federal Regulations (CFR). The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IP(s), and their specific duties within the context of the study. Investigators are responsible for providing Mayne Pharma LLC with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all

documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Premier Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Premier Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Premier Research

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory/GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening Visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4. Study Documents

All documentation and material provided by Mayne Pharma LLC for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The informed consent forms are submitted with this protocol.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent forms and ask questions before signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory/Good Clinical Practice Documents

The regulatory/GCP documents are listed below.

- Signed original protocol (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and subinvestigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form Signature Log/Delegation of Study-related Duties
- Approved ICF and subject materials
- FDA1572 and financial disclosure forms, as applicable (US sites)
- Any other relevant GCP documents

The regulatory/GCP documents must be received from the investigator and reviewed and approved by Mayne Pharma LLC or its designee before the study site can initiate the study and before Mayne Pharma LLC will authorize shipment of IP to the study site. Copies of the investigator's regulatory/GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the trifarotene (CD5789) Cream IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and IP accountability records should also be retained as part of the investigator's regulatory/GCP documents. It is the investigator's responsibility to ensure that

copies of all required regulatory/GCP documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.5. Data Quality Control

Mayne Pharma LLC and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

Mayne Pharma LLC and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Mayne Pharma LLC personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures

- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF will be provided to the sites. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Mayne Pharma LLC or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan (CMP).

14.5.2 Data Management

Mayne Pharma LLC or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data management plan (DMP) will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries will be provided to the sites.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Mayne Pharma LLC or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or clinical study report [CSR])

Mayne Pharma LLC or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Mayne Pharma LLC immediately.

14.6. Study Termination

The study may be terminated at Mayne Pharma LLC's discretion at any time and for any reason.

The DSMB may recommend discontinuation of the study if they find evidence of unacceptable risk to subjects.

14.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, Mayne Pharma LLC or designee will notify the IECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

14.6.2 Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by Mayne Pharma LLC, IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Mayne Pharma LLC or its designee will notify the IECs and regulatory authorities about the premature termination as required according to national laws and regulations. Mayne Pharma LLC or its designee must clearly explain the reasons for premature termination.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the IND or IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is terminated prematurely, all investigators have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Follow-up Visit.

The study might resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or FDA.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. Mayne Pharma LLC may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1 Record Retention

For sites in the US, the investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until 1 of the following occurs:

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

Outside of the US, after completing the study, Mayne Pharma LLC will receive the original eCRFs or at least a legible copy and retain the documents for at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

14.7.2 Sample Retention

Blood samples will be used for purposes related to this study only, and will not be stored for future research. The samples will be stored until they are no longer needed, and the decision has been

made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

Data collected for this study will be analyzed and stored at Premier Research.

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Mayne Pharma LLC. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9. Use of Information and Publication

All information concerning trifarotene (CD5789) cream HE1, Mayne Pharma LLC's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Mayne Pharma LLC or its designee to the investigator, and not previously published, is considered confidential and remains the sole property of Mayne Pharma LLC. Case report forms also remain the property of Mayne Pharma LLC. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by Mayne Pharma LLC in connection with the continued development of trifarotene (CD5789) cream HE1 and thus, may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Mayne Pharma LLC. Publication or other public presentation of trifarotene (CD5789) cream HE1 data resulting from this study requires prior review and written approval of Mayne Pharma LLC. Abstracts, manuscripts, and presentation materials should be provided to Mayne Pharma LLC for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until Mayne Pharma LLC has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

15. FINAL CLINICAL STUDY REPORT

Mayne Pharma LLC will retain ownership of the data.

The final CSR will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

16.2. Subject Information and Informed Consent

A properly constituted, valid IRB or IEC must review and approve the protocol, the investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed consent prior to enrollment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Mayne Pharma LLC, and/or the sponsor's designee. Collection of informed consent has to be documented in the eCRF.

Furthermore, the subject will be informed that if he or she wishes to drop out or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

16.3. Approval by Institutional Review Board and Independent Ethics Committee

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's or the sponsor's representative before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must follow local country requirements.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by Mayne Pharma LLC before implementation.

16.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

17. REFERENCES

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18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER:	18-ICH-001
PROTOCOL TITLE:	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
FINAL PROTOCOL DATE:	v3.0 for Ukraine, 21-Nov-2019

The undersigned acknowledges possession of and has read the product information (e.g., investigator's brochure) on the IP and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected subjects in his/her care, according to the study protocol.

He or she agrees to use the study material, including IP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Mayne Pharma LLC.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Mayne Pharma LLC within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IP.

He or she agrees to comply with Mayne Pharma LLC and regulatory requirements for the monitoring and auditing of this study. In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

APPENDICES

A. Regulations and Good Clinical Practice Guidelines

A. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives (and applicable regulations/guidances):

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents>

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

PROTOCOL/CLINICAL INVESTIGATION PLAN

PRODUCT NAME/NUMBER:	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER:	18-ICH-001
IND NUMBER:	140538
NCT NUMBER:	NCT03738800
EUDRACT NUMBER:	2018-003272-12
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
PROTOCOL DATE: AMENDMENT DATE:	Final v1.0, 28-Nov-2018 Final v2.0 for Ukraine, 21-Oct-2019
COORDINATING/PRINCIPAL INVESTIGATOR:	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine, PO Box 208059 333 Cedar Street New Haven, CT 06520, USA Phone: +1 203 789 1249
SPONSORED BY:	Mayne Pharma LLC 1240 Sugg Parkway Greenville, NC 27834, USA Phone: +1 984 242 1400
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive, Suite 150 Durham, NC 27709, USA Phone: +1 919 627 9100

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: 18-ICH-001

PROTOCOL TITLE: A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale

I, the undersigned, have read this protocol and confirm that to the best of my knowledge, it accurately describes the planned conduct of the study.

SIGNATURE **DATE:**

22/Oct/2019

Ilana Stancovski, PhD
Chief Scientific Officer
Mayne Pharma LLC

DocuSigned by:
Phoevos Hughes
Signer Name: Phoevos Hughes
Signing Reason: I approve this document
Signing Time: 22-Oct-2019 | 10:31:05 PDT
2D31DD1CA65A48718371307AF875E4CE

22-Oct-2019 | 10:31:09 PDT

Phoevos Hughes, JD
Associate Director, Clinical Operations
Mayne Pharma LLC

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Marlis Sarkany
Signer Name: Marlis Sarkany
Signing Reason: I approve this document
Signing Time: 23-Oct-2019 | 07:38:03 EDT
16E1C8AEDC854CDC86688C1FD466E26F

23-Oct-2019 | 07:38:15 EDT

Marlis Sarkany, MD
Senior Medical Director
Premier Research

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Signer Name: Adrienne Kuxhausen
Signing Reason: I approve this document
Signing Time: 22-Oct-2019 | 13:24:50 EDT
6E6B87C6B98740819F26B8D5A7D662CF

22-Oct-2019 | 13:24:52 EDT

Adrienne Kuxhausen, MS
Senior Biostatistician
Premier Research

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER	18-ICH-001
EUDRACT NUMBER	2018-003272-12
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, and Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
INDICATION	Lamellar ichthyosis
OBJECTIVES	Primary: To compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in subjects with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 12 weeks of treatment. Secondary: • To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% body surface area (BSA) twice weekly. • To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.
STUDY DESIGN	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Visual Index for Ichthyosis Severity (VIIS) for scaling where 0 = clear and 4 = severe) on at least 2 areas of the 4 body areas assessed (chest/abdomen, back, arms, and legs). Subjects in Cohorts A and B will be subsequently randomized in a double-blind fashion to 1 of 2 doses of trifarotene cream HE1 or vehicle and treated twice weekly for 12 weeks. Subjects who complete the randomized, Double-blind Period of the study will be eligible to enter a 12-week, Open-label Extension (OLE) Period in which additional PK, safety, and efficacy data will be collected. Approximately 15 subjects will be randomized into the first cohort of subjects (Cohort A) in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks. After the initial 15 subjects complete at least 28 days of treatment, an independent Data Safety Monitoring Board (DSMB) will review aggregate safety and tolerability data. If no safety issues are identified, an additional group of about 105 subjects will be allowed to enroll in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks in the same manner as subjects in Cohort A. All subjects who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE Period. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for up to 12 weeks. After Screening, eligible subjects for Cohort A and B will enter a washout period of up to 35 days, during which they must stop using the following prohibited medications:

a. Topical treatments

Medication	Washout Period
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	-

b. Systemic treatments

Medication	Washout Period
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines (except Vitamin D analogues taken at stable dose since at least 1 month)	8 weeks
QT prolonging drugs	5 half lives
Enzymatic inductors (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (not all inclusive: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives

Study drug will be packaged in 50-g tubes from which up to 36 g of investigational product (IP) may be dispensed per application, i.e., the maximum dose per application. Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied.

Thereafter, each subject will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of product in a tube. Subjects will record the date and time of study treatment administration in the subject diary.

Local tolerability may differ in subjects with LI compared to healthy subjects, as their skin is drier and may be more sensitive. Local tolerability will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., on Day 7 and Day 45 in the Double-blind Period; at Day 97 and 134 in the OLE Period) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability (Scale: 0–3 [none, mild, moderate, severe] for stinging/burning, pruritus, erythema) on each body area (chest/abdomen, back, arms, and legs) and the following procedures will be followed:

- If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2;

	• If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3. Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and adverse events (AEs). All subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]) and any AEs, including application site reactions and concomitant medications used. Subjects will also be advised on permitted emollient(s) use on nontreatment days during the study; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Photographs will be taken at Baseline, on Day 30 and Day 90 at selected sites with photographic capability for subjects who sign a separate photographic informed consent form (ICF). Samples for pharmacokinetic (PK) analysis will be drawn from all subjects at Baseline and at each clinic visit. In addition, a PK substudy is to be conducted at a limited number of sites. Participation in the PK substudy will be optional and will include at least 30 subjects. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for these subjects at each of the other clinic visits. Subjects who complete the Double-blind Treatment Period will have the option to continue into the OLE to assess safety for an additional 12-weeks with trifarotene cream HE1 200 µg/g twice weekly, on up to 90% of BSA, sparing the scalp, inguinal, and axillary areas. During the OLE Period, subjects will return to the site at Weeks 14, 16, 20, 24, and 26 for safety, tolerability, and efficacy assessments. Blood samples will be drawn for clinical laboratory safety tests and PK at Weeks 16 and 24. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 97 and Day 134) to assess safety; an unscheduled clinic visit may be performed, if necessary.
PLANNED NUMBER OF SUBJECTS	Approximately 120 total subjects; 15 subjects in Cohort A and 105 subjects in Cohort B.
STUDY ENTRY CRITERIA	Inclusion criteria: 1. Subject is ≥18 years old. 2. Subject has known diagnosis of LI. 3. Subject has moderate to severe (VIIS 3-4) LI on at least 2 of the 4 body areas assessed (chest/abdomen, back, arms, and legs). 4. Subject has signed an ICF at Screening before any investigational procedures. 5. Subject who is participating in photography has signed a photography ICF. 6. Subject who is participating in the optional PK substudy has signed a PK ICF. 7. Subject is not of childbearing potential, i.e., a female who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason, hysterectomy or bilateral oophorectomy), OR • Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception:

	• bilateral tubal ligation • combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline OR Agrees to abstain from sex during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. AND Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application. 8. Women of child-bearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine). 9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent. 10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin). Exclusion criteria: 1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization including syndromic ichthyoses. 2. Subject has a history of or current moderate or severe stinging/burning at Screening. 3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments. 4. Subject with a known lipid disorder unless well controlled by stable doses of lipid-lowering agents for at least 6 months. 5. Subject was previously treated with trifarotene/CD5789, including the acne formulation, or participated in previous studies for ichthyosis. 6. Subject has known skeletal disease, hypertriglyceridemia, hypercholesterolemia, liver disease, or other poorly controlled medical conditions. 7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome), Crohn's disease, or any other significant concomitant disease other than LI that, in the investigator's opinion, may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 8. Subject is being treated for major depression disorder. 9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening. 10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory b. Triglycerides >200 mg/dL c. Total cholesterol >250 mg/dL d. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women e. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L.

	11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 12. Subject has a history of long QT syndrome or clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, QTcF interval >450 ms, PR interval is not between 120 and 220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed. 13. Subject has a known allergy or sensitivity to any of the components of the investigational products. 14. Subject has been exposed to excessive ultraviolet (UV) radiations on the treated zones within 1 month before Baseline visit or who is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.). 15. Subject is inherently sensitive to sunlight. 16. Subject is presumed to be abusing drugs or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms. 17. Subject is participating in another interventional clinical trial.
INVESTIGATIONAL PRODUCT	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 200 µg/g applied topically twice weekly on up to 90% BSA
REFERENCE PRODUCT	Name: Vehicle cream Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) applied topically twice weekly on up to 90% BSA
TREATMENT REGIMENS	Topical application twice weekly to all affected skin except the scalp, axillae, and inguinal area.
COORDINATING/ PRINCIPAL INVESTIGATOR	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine New Haven, CT 06520, USA
PLANNED STUDY SITES	Approximately 40 sites across North America, Europe, Israel, and Australia

CRITERIA FOR EVALUATION	Primary efficacy endpoint: The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0-4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs). Secondary endpoints: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices: – Investigator's Global Assessment (0-4) for each body area – Palm/sole Assessment (Scale: 0–4) – Individual score for roughness (Scale: 0–4) overall • Quality of life per Dermatology Life Quality Index (DLQI) • The difference in proportion of subjects with presence of fissures (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) between the active trifarotene cream HE1 and vehicle groups Exploratory endpoints: • The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups • Quality of life per EQ-5D-5L Safety endpoints: • Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs • Local tolerability (Scale: 0–3 [none, mild, moderate, severe], determined by the investigator) on each of the 4 body areas (chest/abdomen, back, legs, arms) Pharmacokinetic endpoints: Plasma concentrations of CD5789 and its major metabolites will be measured.
STATISTICAL METHODS	Analysis Populations: The following are planned for the Double-blind Period of the study: The Safety population will be the primary population for analyses of safety and tolerability and will comprise all subjects who are randomized to treatment and receive at least 1 application of study drug. The intent-to-treat (ITT) population will comprise all randomized subjects. The modified intent-to-treat (mITT) population comprises all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The per-protocol (PP) population will be defined prior to database lock and will comprise subjects in the mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations. The PK population includes all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. The PK population will be used to summarize all PK endpoints.

	The following populations are planned for the OLE period of this study: The OLE Safety population: all subjects who complete the 12-week Double-blind Treatment Period and receive at least 1 application of study drug in the OLE Period. OLE ITT population: all subjects who complete the 12-week Double-blind Period and who sign the OLE informed consent. The OLE mITT population: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6. The OLE PP population: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study. Subject Characteristics and Disposition: Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and baseline characteristics for all enrolled subjects. Medical history, physical examination findings, and vital sign measurements for all randomized subjects will be presented in listings. Efficacy Analyses: The number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT in the Double-blind Period will be presented. Generalized estimating equations (GEE) for binary response will be used to model the odds of successful resolution of LI with treatment group as a predictor. Other covariates, such as baseline VIIS scores, baseline characteristics, and interactions may be included. Various correlation matrix structures will be explored to model the within subject correlation. Additionally, the difference in mean VIIS score at Week 12/EOT between the active trifarotene cream HE1 groups and vehicle group will be analyzed using a 2-sided, 2-sample Wilcoxon rank-sum test at the 5% significance level; 95% confidence intervals will be presented. The VIIS scores as well as secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Week 24. Change from Baseline through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from Baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and Baseline score value as a covariate. Frequencies of results and 95% confidence intervals will also be reported, and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test. For subjects who report having fissures, the number of fissures and pain related to fissures will also be presented on a scale of 0–3 (none, mild, moderate, severe). Clinical Pharmacology Analyses: Noncompartmental PK analysis will be performed for the PK subset of subjects, as data permit. Plasma concentrations of CD5789 and its major metabolites will be measured and will be listed by subject. Safety Analyses: Safety and tolerability will be assessed based on the incidence of reported TEAEs, and SAEs, including relationship to study drug and severity, as well as physical examination findings, vital sign measurements (supine systolic blood pressure [SBP] and diastolic blood pressure [DBP] and pulse), clinical laboratory results (hematology, including serum aminotransferases and serum lipids, coagulation, clinical chemistry, and urinalysis) and 12-lead ECGs. Descriptive statistics for observed values and change from Baseline will be calculated at each visit within each study period and by treatment group within cohort.

SAMPLE SIZE DETERMINATION	The first cohort of 15 subjects is a reasonable sample size to assess safety and tolerability before enrolling additional subjects in Cohort B. Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) using a 2-sample t-test, assuming a mean difference of at least 1.0 and a standard deviation of 1.4 or lower. This study is not powered to detect a difference between the 2 active arms.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study will be as follows: 1. Screening and Washout: Up to 35 days (≥2 weeks washout for topical keratolytics, including urea and salicylic acid, and any topical retinoid or retinol [Vitamin A derivative], and ≥4 weeks washout for oral Vitamin A). 2. Double-blind study drug application: Twice weekly for up to 12 weeks. 3. Optional Open-label Treatment: Twice weekly for up to 12 weeks. 4. Follow-up: 14 days after last study drug application. The maximum study duration for each subject is approximately 229 days (33 weeks). The maximum treatment duration for each subject is 24 weeks.

2.2. Schedule of Events

Table 2-1: Schedule of Events for Double-blind Period

	Screening (-35 days to -1 day)	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[a,b] ± 7 days (ET)
Visit	**1**	**2**		**3**	**4**		**5**	**6**
Week		**1**		**2**	**4**		**8**	**12**
Written informed consent	X							X[a]
Assign screening number	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical history	X							
Physical examination[c]	X	X						X
VIIS[d] assessment	X	X		X	X		X	X
Assign randomization number		X						
IGA assessment	X	X		X	X		X	X
Palm/sole assessment	X	X		X	X		X	X
Roughness, fissuring assessment[e]	X	X		X	X		X	X
Ectropion score	X	X		X	X		X	X
Photographs[f]		X			X			X
Quality of life per Dermatology Life Quality Index (DLQI)		X		X	X		X	X
EQ-5D-5L Quality of Life Questionnaire		X		X	X		X	X
Vital signs (blood pressure and pulse)	X	X		X	X		X	X
Height, weight, and BMI		X						X

	Screening (-35 days to -1 day)	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[a,b] ± 7 days (ET)
Visit	**1**	**2**		**3**	**4**		**5**	**6**
Week		**1**		**2**	**4**		**8**	**12**
12-lead ECG[g]	X	X			X			X
Clinical laboratory tests (hematology, chemistry, urinalysis)[h]	X	X			X			X
Serology (hepatitis B surface antigen, hepatitis C)	X							
Pregnancy test for female subjects (serum at Screening; urine subsequently)	X	X			X		X	X
Assign randomization number		X						
PK blood sample collection[i]		X		X	X		X	X
Initial study drug application by clinic staff and measurement[j]		X						
Application instructions, advice on emollient use		X	X	X	X	X		
Dispense study drug and diaries[k]		X		X	X		X	
Concomitant medications	X	X	X	X	X	X	X	X
Tolerability assessment		X		X	X		X	X
Adverse events (and review diaries)		X	X	X	X	X	X	X
Collect all used/unused study drug[l]				X	X		X	X
Provide information about OLE option					X	X	X	

Abbreviations: BMI = body mass index; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears, nose, throat; ICF = informed consent form; IGA = Investigator Global Assessment; OLE = open-label extension; PK = pharmacokinetic; WOCBP = women of childbearing potential; VIIS = Visual Index for Ichthyosis Severity

a. Day 90 procedures should be conducted for subjects who terminate the study early. If a subject discontinues IP, but continues to attend clinic visits, Day 90 will occur as scheduled. Day 90/Week 12 will be the first visit of the OLE Period for subjects who choose to continue (subjects will have up to 7 days to

decide to sign the ICF and begin the OLE). Subjects who decide to continue into the OLE will have the following additional procedures: 1) sign informed consent; 2) will be weighed; 3) will be instructed on study drug application; 4) will be given new diaries, and 5) will be provided with study drug.

b. A Follow-up telephone call will be made within 14 days after Day 90 to subjects who choose not to continue into the Open-label Extension.
c. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
d. VIIS: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe for each of 4 body areas: chest/abdomen, back, arms, and legs (possible overall score = 16).
e. Roughness (0-4 scale); fissuring assessment: present/absent/number/pain (0-3 scale).
f. Photography will be performed at sites with the capability among subjects who sign a photographic ICF.
g. ECG to be conducted at Screening, Baseline, Day 30, and Day 90 for all subjects.
h. Subjects must be fasting (i.e., at least 8 hours)
i. Samples for PK will be drawn from all subjects at Baseline and at each clinic visit. At selected sites among subjects who consent to participate in the PK-substudy, samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1. On Day 30, IP will be applied in the clinic for PK substudy subjects, and PK samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose. Trough levels will be drawn when the subjects are in the clinic for other study visits (i.e., Day 14, Day 60, and Day 90).
j. Study staff will apply initial dose of study drug in the clinic after Baseline measurements, and the amount of study drug used will be measured (i.e., 36-g tube will be measured before and after application to determine amount used) to determine fixed dose.
k. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug tubes before dispensing; subjects must record days/times of study drug application in the diaries and any areas of skin not treated, e.g., due to local reactions). Dispense enough additional study drug until next visit (except at Day 90, unless subject consents to continue into OLE).
l. Confirm study drug compliance by measuring tube weight and reviewing diary.

Table 2-2: Schedule of Events for Open-label Extension

	Open-label Treatment Period						Follow-up
	Telephone Visit (Day 97)[a]	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7**	**8**		**9**	**10**	**11**
Week		**14**	**16**		**20**	**24**	**26**
Informed consent[a]							
Physical examination[b]						X	X
ECG			X			X	
VIIS[c] assessment		X	X		X	X	X
IGA assessment		X	X		X	X	X
Palm/sole assessment		X	X		X	X	X
Roughness, fissuring assessment[d]		X	X		X	X	X
Ectropion score		X	X		X	X	X
Vital signs (blood pressure and pulse)		X	X		X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)[e]			X			X	
Pregnancy test for female subjects (urine)			X		X	X	X
PK blood sample collection[f]			X			X	
Application instructions, advice on emollient use[g]	X	X	X	X			
Dispense study drug and diaries[h]		X	X		X		
Concomitant medications	X	X	X	X	X	X	X
Tolerability assessment		X	X		X	X	
Adverse events (and review diaries)	X	X	X	X	X	X	X

	Open-label Treatment Period						**Follow-up**
	Telephone Visit (Day 97)[a]	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7**	**8**		**9**	**10**	**11**
Week		**14**	**16**		**20**	**24**	**26**
Collect all used/unused study drug[i]		X	X		X	X	

Abbreviations: ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears, nose, throat; IGA = Investigator Global Assessment; PK = pharmacokinetic; VIIS = Visual Index for Ichthyosis Severity; WOCBP = women of childbearing potential

a. Subjects will sign the OLE ICF at the Double-blind Day 90/Week 12 Visit or within 7 days thereafter. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing and PK from Day 90/Week 12 will be carried over for the OLE Period and will not be repeated.
b. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
c. VIIS: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe for each of 4 body areas: chest/abdomen, back, arms, and legs (possible total score = 16).
d. Roughness (0-4 scale); fissuring assessment: present/absent/number/pain (0-3 scale).
e. Subjects must be fasting (at least 8 hours)
f. Samples for PK will be drawn from all subjects on Day 120 and Day 180.
g. Subjects must record days/times of study drug application in the diaries and any areas of skin not treated (e.g., due to local reactions).
h. All subjects in the open-label extension will receive trifarotene 200 µg/g. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug tubes before dispensing. Dispense enough additional study drug until the next visit (except on Day 180).
i. Confirm study drug compliance by measuring tube weight and reviewing diary.

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

3.2. List of In-Text Figures

SUMMARY OF AMENDED SECTIONS

All references to “adults/adolescents” have been changed to “subjects” throughout the protocol.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ATC	anatomical therapeutic chemical
AUC	area-under-the-curve
BMI	body mass index
BSA	body surface area
CFR	code of federal regulations
CI	confidence interval
C_{max}	maximum concentration
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressure
DLQI	dermatology life quality index
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ESS	ectropion severity score
FDA	Food and Drug Administration
GCP	good clinical practice
GEE	generalized estimating equations
HR	heart rate
IB	investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IND	investigational new drug
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat

ABBREVIATION	EXPLANATION
IUD	intrauterine device
IWRS	interactive web response system
LI	lamellar ichthyosis
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
MMRM	mixed model of repeated measures
NCA	noncompartmental analysis
OC	observed case
OLE	open-label extension
PG	propylene glycol
PK	Pharmacokinetic(s)
PoC	proof-of-concept
PP	per-protocol
QTc	QT interval corrected for heart rate
RARγ	retinoid acid receptor γ
RBC	red blood count
RR	respiratory rate
RXR	retinoid X receptor
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
TEAE	treatment-emergent adverse event
T_{max}	time of C_{max}
UAE	unexpected adverse event
UADR	unexpected adverse drug reaction
US	United States
UV	ultraviolet
VIIS	Visual Index for Ichthyosis Severity
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of child-bearing potential

5. INTRODUCTION

5.1. Background and Rationale

The ichthyoses comprise a large group of skin scaling disorders with diverse etiology. The stereotypic pathophysiology is epidermal hyperplasia and the formation of excess stratum corneum accompanied by abnormal (delayed and/or disordered) desquamation, with visible accumulation of squames (scales) on the skin's surface – the clinical hallmark of all the ichthyoses.

Lamellar ichthyosis (LI) is recognized as a severe form of ichthyosis that persists throughout life. During the first postnatal weeks, the hyperkeratotic membrane patients are typically born with is gradually shed, and is replaced by scaling and lichenification that involves the entire body including the intertriginous areas, palms, soles, and scalp. While usually not life threatening, LI can result in disability, partial deafness, poor adaptation to environmental conditions (due to hypohydrosis), severe discomfort (pruritus, fissuring of the skin) and significant psychosocial impact.

Lamellar ichthyosis, a member of the nonsyndromic autosomal recessive congenital ichthyosis group of ichthyoses, has an incidence of 1 per 100,000–300,000 live births.[1] Lamellar ichthyosis is undoubtedly a rare disease.

Therapeutic approaches for LI are mainly based on the use of topical emollients, keratolytic agents (urea, lactic acid, salicylic acid), topical retinoids and, in severe cases, oral retinoids.[2,3]

Oral retinoid usage in LI is mainly based on case reports and case series.[4,5,6,7,8] The mechanism of retinoid action involves modulation of keratinocyte differentiation, keratinocyte hyperproliferation and tissue infiltration by inflammatory cells. Systemic retinoids (such as acitretin, etretinate, or isotretinoin) have been found to be efficacious in the treatment of severe ichthyoses, especially in LI.[6]

Vahlquist, et al (2008)[3] report that by combining 2 or more keratolytic agents and moisturizers in the same lipophilic cream base, it is often possible to achieve additive or even synergistic effects in LI without the need to use irritating concentrations of either agent alone. In a double-blind trial of 4 different cream mixtures in 20 patients with LI, a mixture of 5% lactic acid and 20% propylene glycol (PG) in a semi-occlusive cream for 4 weeks twice daily was significantly more effective than 20% PG or 5% urea alone in the same vehicle.[9] Although the treatments were well tolerated, an efficient removal of hyperkeratosis without correcting the underlying biochemical defect in LI is likely to deteriorate the patient's intrinsic barrier problem, because an excessive production of corneocytes probably represents a homeostatic response to an ineffective barrier. Indeed, transepidermal water loss increased after successful treatment of LI with either topical keratolytics[9] or oral retinoid.[10] Although this may not be noticeable by the patient, even minor deteriorations in the barrier function can enhance transcutaneous penetration of active cream ingredients or other topically applied chemicals, which is a matter of special concern in children. Accordingly, α-hydroxy acids and salicylic acid should not be used at all in babies and only with great caution when treating large, eroded skin areas in adult patients.[11,12]

Many patients with LI use pumice, foot files, or gentle rubbing of the skin after a hot bath or a shower to remove scales and hyperkeratosis. Overnight occlusion of problematic skin areas with plastic sheets after applying a thick layer of emollient or keratolytic agents is another way of potentiating therapy, especially on the scalp, which is notoriously difficult to treat. Although

usually effective, all these remedies may further damage the skin barrier and lead to exaggerated epidermal proliferation, erythema, painful erosions and increased transcutaneous penetration.[3]

Based on this information, LI has significant unmet medical need for safer and more effective therapies.

5.1.1. CD5789 (Trifarotene)

CD5789 is a new chemical entity discovered by Galderma R&D SNC and formulated for topical application. It is a novel retinoid acid receptor γ (RARγ) agonist, characterized by its high specificity to this receptor. CD5789 is selective for RARγ over RARα and RARβ (approximately 50- and 8-fold, respectively), with no retinoid X receptor (RXR) activity. CD5789 is currently under clinical development for the topical treatment of various dermatoses, including acne vulgaris and LI.

The pharmacological retinoid-like properties of CD5789 were confirmed in in vitro and in vivo models, showing its interest for its development in the treatment of LI. Therefore, it may have an effect on the differentiation and hyperproliferation of keratinocytes, and consequently improve hyperkeratotic skin of patients with LI.

Within the overall acne development program at Galderma, CD5789 has been tested in different pharmaceutical forms for topical administration. As of 15-Jan-2018, 6 different formulations have been evaluated: a solution, a gel and 4 creams (CD5789 cream A, CD5789 cream B, CD5789 cream HE1 concept and its optimized version, cream HE1), with different concentrations (up to 400 µg/g). Therefore, several formulations at different CD5789 concentrations have been tested in nonclinical and clinical development programs.

Galderma decided to develop a new cream formulation that might better address the issue of skin dryness in patients with LI. This formulation was named “Cream HE1 concept.” It has been preliminarily investigated in an exploratory trial in psoriasis at concentrations up to 400 µg/g (RD.03.SRE.40204E). In a proof-of-concept study (RD.03.SRE.40181E), positive results were also obtained in patients with LI with CD5789 cream (up to 100 µg/g) that was effective in decreasing scaling and roughness. Based on these results, a new CD5789 formulation (cream HE1) was developed for further clinical investigations in LI. The formulation cream HE1 was developed with the objective to obtain a formulation with appropriate stability of the active ingredient and in which CD5789 would be homogeneously dissolved in the oily phase at a higher concentration compared to the cream formulation used in the acne program. Cream HE1 contains 100, 200, or 400 µg/g (0.01% [w/w], 0.02% [w/w], 0.04% [w/w], respectively) of CD5789.

Galderma has granted Mayne Pharma LLC an exclusive license to develop and commercialize CD5789 (trifarotene) for LI and other orphan diseases; therefore, the LI indication is no longer pursued by Galderma.

5.2. Clinical Experience

The cream HE1 differs from the CD5789 cream used to treat acne vulgaris in that it contains fewer excipients with drying effects and therefore may be better suited for patients with LI.

Throughout the 30 clinical studies that comprise the clinical development program for CD5789 topical products, 1976 subjects were exposed to CD5789. No systemic safety concerns related to CD5789 gel or creams, or cream HE1 at doses up to 400 µg/g were reported. The subjects

were exposed to a maximal total CD5789 dose of 36 g/day (Investigator's Brochure [IB] for CD5789 Cutaneous Formulation).

The CD5789 PK profile was also investigated using cream HE1 (Study GD.03.SRE.103813) in 36 healthy volunteers of Japanese and non-Japanese origin. Subjects were treated daily on up to 90% of body surface area (BSA) for 29 days with up to 36 g of cream formulation. Both CD5789 100 µg/g and 200 µg/g cream HE1 were investigated. Plasma PK assessment demonstrated that repeated topical applications of CD5789 cream HE1 resulted in low and similar CD5789 systemic levels in all treatment groups. In addition, no systemic safety concerns were raised from this healthy volunteer study in which cream HE1 200 µg/g was applied daily under maximal-use conditions on almost the full body. In this study, however, the level of irritation resulted in the need to decrease the frequency of application to twice weekly (IB for CD5789 Cutaneous Formulation).

5.3. Summary of Potential Risks and Benefits

Although the primary objective of this study is safety in the patient population with LI, the potential benefits of study participation are that subjects with LI may experience a reduction in their LI symptoms as a result of treatment with trifarotene (CD5789) cream HE1. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to trifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture.

Animal studies with CD5789 have shown reproductive toxicity in the embryo-fetal studies. Despite low systemic levels with the CD5789 concentration of 50 µg/g used in patients with acne, CD5789 must not be administered during pregnancy.

When CD5789 is used in the other formulations and/or for other indications and/or with higher concentrations or higher application surface areas, the potential risk of teratogenicity needs to be considered as the safety margin may be lower. Depending on the study population and conditions mentioned above, or other specific requirements, the appropriate contraception method is described in this protocol.

It is unknown whether CD5789 or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Lactating women are not eligible for the clinical study.

Certain cutaneous signs and symptoms of irritation and localized reactions at the application site such as erythema, scaling, dryness, stinging/burning, and pruritus may be experienced with use of CD5789. Depending upon the severity of these side effects, subjects may be instructed to reduce the frequency of application or to discontinue use.

Trifarotene cream contains propylene glycol that is mildly irritant to the skin, eyes, and mucous membranes. Trifarotene (CD5789) cream HE1 also contains butylated hydroxytoluene that may cause local skin reactions (e.g., contact dermatitis), or irritation to the eyes and mucous membranes and sodium benzoate that is mildly irritant to the skin, eyes, and mucous membranes.

CD 5789 is mildly irritant to the skin, eyes, and mucous membranes. Therefore, it should not come into contact with the eyes, mouth, or mucous membranes.

There is a potential risk of skin sensitization. If a reaction suggesting sensitivity to trifarotene (CD5789) cream HE1 occurs, the use of the trifarotene cream HE1 must be discontinued.

There is a potential risk of photosensitivity disorder (sunburn). Excessive exposure to sunlight or ultraviolet (UV) radiation (i.e., occupational exposure to the sun, planned holidays in the sun during the study, phototherapy, tanning salon) must be avoided during the studies.

As reported with other topical retinoids, there is a potential risk of pigmentation disorders.

A summary of the pharmaceutical properties and known potential risks of trifarotene (CD5789) cream HE1 is provided in the current version of the IB. The investigator must become familiar with all sections of the trifarotene (CD5789) cream IB before the start of the study.

6. OBJECTIVES

6.1. Primary Objective

The primary objective is to compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in subjects with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as LI after 12 weeks of treatment.

6.2. Secondary Objectives

The secondary objectives are as follows:

- To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% BSA twice weekly.
- To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.

7. STUDY DESIGN

7.1. Overall Study Design and Plan

The first part of this study is a phase 2, randomized, 2-cohort, double-blind, vehicle-controlled, multicenter study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in subjects with LI. Subjects who complete the randomized, double-blind, vehicle-controlled period of the study will be eligible to continue into an open-label extension (OLE) period and be treated with trifarotene cream HE1 200 µg/g for an additional 12 weeks.

The randomized, double-blind, vehicle-controlled period of the study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Visual Index for Ichthyosis Severity [VIIS] index for scaling where 0 = clear and 4 = severe on at least 2 of 4 areas of the body: chest/abdomen, back, arms, and legs), is designed to compare the safety of 2 doses of trifarotene cream HE1 with that of vehicle in the treatment of LI.

After Screening, eligible subjects for Cohorts A and B will enter a washout period of up to 35 days, during which they must stop using prohibited topical and systemic treatments with designated washout periods (Table 9-1).

The first cohort of subjects (Cohort A) will randomize approximately 15 subjects in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle.

Study drug will be packaged in 50-g tubes from which up to 36 g of IP may be dispensed per application, i.e., the maximum dose per application. Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied (i.e., study staff will measure the 50-g tube before and after the first application to determine the fixed dose amount for each subject). Thereafter, subjects will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of IP in a tube.

Subjects enrolled in Cohort A will continue treatment for up to 12 weeks.

After the initial 15 subjects complete at least 28 days of treatment, an independent Data Safety Monitoring Board (DSMB) will review aggregate safety and tolerability data. If no safety issues are identified, additional subjects will be allowed to enroll in Cohort B (up to approximately 105 subjects). Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and similarly treated twice weekly for up to 12 weeks in the same manner as subjects in Cohort A.

Subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]), any application site reactions, adverse events (AEs), and concomitant medications used. Subjects will also be advised on permitted emollient(s) use on nontreatment days during the study; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited.

Photographs will be taken at Baseline, Day 30, and Day 90 in the Double-blind Period at selected sites with photographic capability for subjects who signed a separate photographic informed consent form (ICF).

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit, as indicated in the Schedule of Events (Table 2-1).

In addition, a PK substudy will be conducted at specific sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 30 subjects. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for all subjects at specified time points.

Efficacy will be assessed by the number of subjects in each treatment group who achieve "success" defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0-4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs). In addition, efficacy criteria include assessment of the Investigator Global Assessment (IGA; scale: 0-4 for each body area: chest/abdomen, back, legs, and arms), scales for palm/sole, roughness, fissuring, and the Dermatology Life Quality Index (DLQI), and the EQ-5D-5L Quality of Life (QoL) Questionnaire. Ectropion Severity Scores (ESS) between the active trifarotene cream HE1 and vehicle groups will be an exploratory endpoint.

Plasma concentrations of CD5789 and its major metabolites will be measured.

Safety will be assessed by evaluating reported AEs, changes in clinical laboratory test results, vital sign measurements, physical examinations, 12-lead electrocardiograms (ECGs), and local tolerability.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent through the posttreatment visit) will be documented.

Topical trifarotene cream HE1 was generally well tolerated in recently completed phase 3 pivotal and long-term safety studies in subjects aged 9 years and older with acne vulgaris. The local tolerability of the trifarotene cream HE1 formulation in subjects with LI is unknown and will be monitored during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., on Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability (Scale: 0–3 [none, mild, moderate, severe]) on each body area (chest/abdomen, back, legs, arms) and will follow the procedures detailed in Section 9.4.

Subjects who complete the 12-week Double-blind Treatment Period will have an option to continue into an OLE Period for an additional 12 weeks with trifarotene cream HE1 200 µg/g. During the OLE Period, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and Week 24 from all subjects who continue into the OLE Period (Table 2-2).

Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and AEs; see Section 9.4.

Figure 7-1: Double-blind Study Design

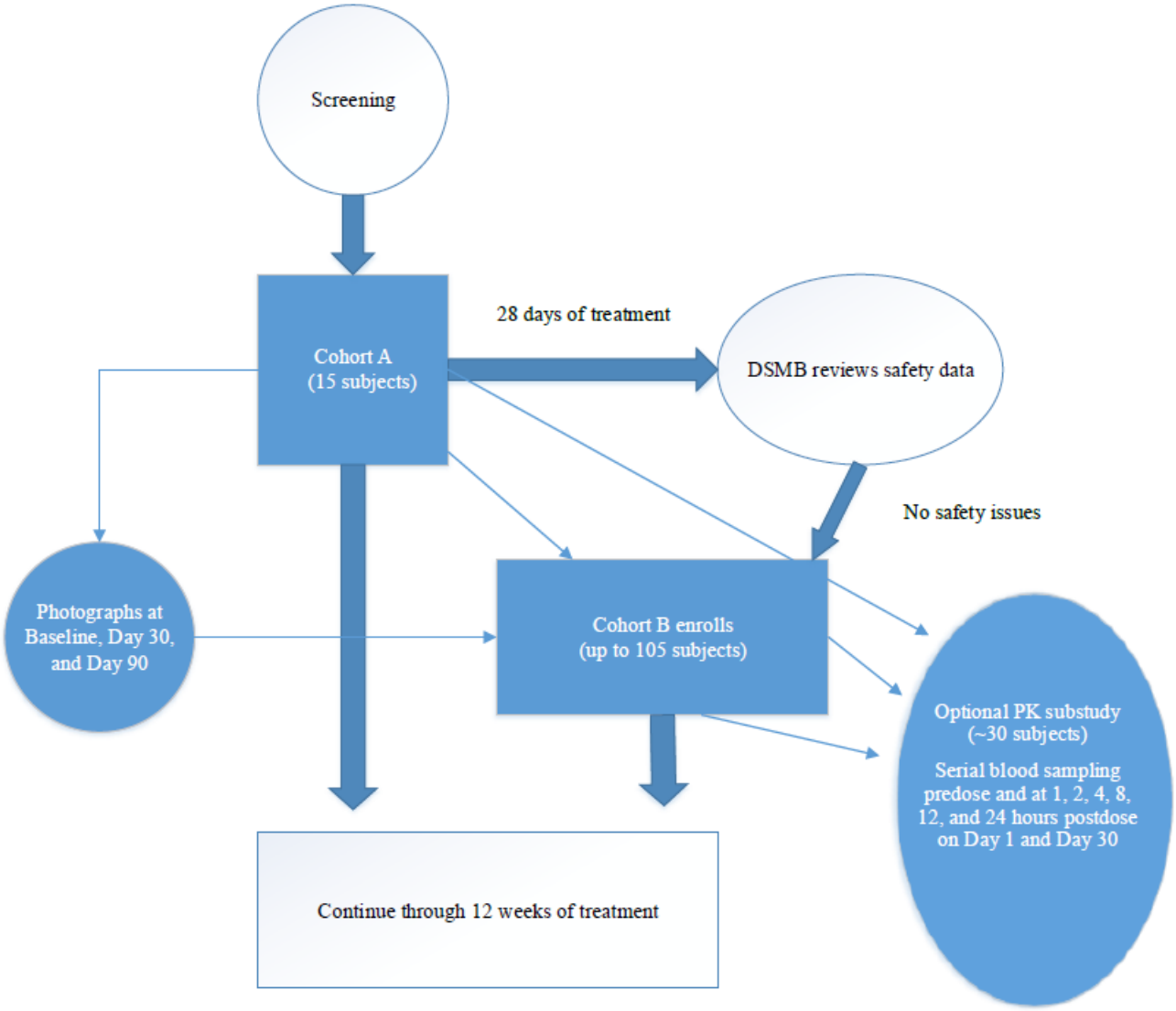
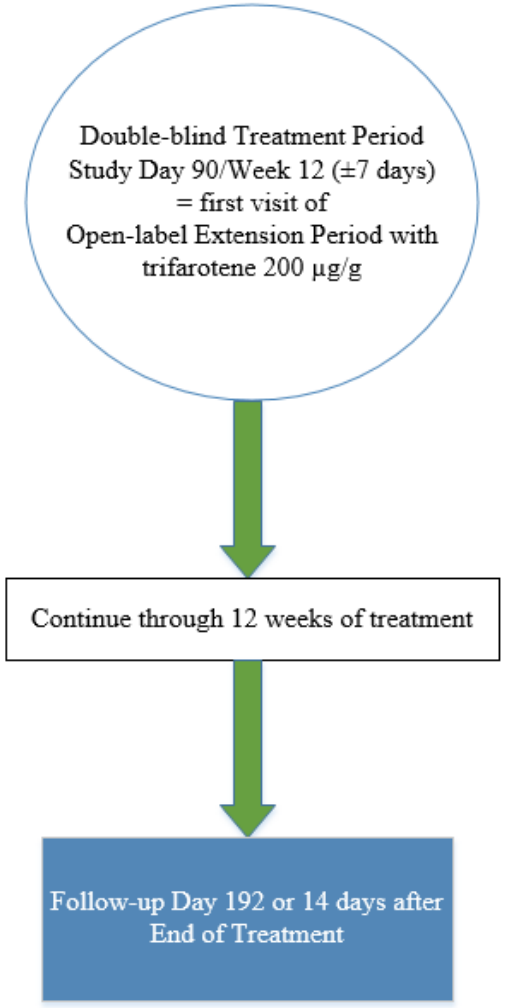


Figure 7-2: Open-label Study Design



7.2. Rationale and Discussion of Study Design

The first part of this study is a randomized, double-blind, placebo-controlled study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in subjects with LI.

In a previous proof-of-concept study (RD.03.SRE.40181E), subjects with LI applied trifarotene 50 and 100 µg/g cream to limited areas, and results demonstrated a decrease in scaling with good safety and tolerance. In a phase 1 study in healthy Japanese and non-Japanese subjects (RD.03.SPR.103813), repeated topical applications of trifarotene (CD5789 cream HE1) 100 µg/g and 200 µg/g resulted in low and similar CD5789 systemic levels in all the cohorts. These studies are fully described in the current IB.

To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of 15 subjects randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly. An independent DSMB will review aggregate safety and tolerability data from the initial 15 subjects' first 28 days of treatment. If no safety issues are identified, and additional group of 105 subjects will be allowed to enroll in Cohort B and will be randomized to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly in the same manner as subjects in Cohort A. All subjects in the randomized, double-blind portion of the study will be treated for up to 12 weeks, and data on safety, tolerability, PK, and efficacy collected.

Subjects who successfully complete the initial 12 weeks of double-blind treatment will have the option to enter an OLE with trifarotene cream HE1 200 µg/g twice weekly for up to 12 weeks.

The OLE will collect additional safety, tolerability, PK, and efficacy data. As designed, this study will provide important information on safety, tolerability, and PK with dosing of subjects with LI for up to 6 months.

The protocol includes appropriate monitoring for safety and tolerability. If subjects develop significant local application site reactions or tolerability issues, the protocol includes language for reducing the frequency of application or halting study drug application until the symptoms abate.

7.3. Selection of Doses in the Study

Based on the results from Study RD.03.SRE.40181E and Study SRE.103813, the doses of 100 µg/g and 200 µg/g were selected for further investigation in subjects with moderate to severe LI. The PoC study demonstrated efficacious treatment with 100 µg/g of trifarotene cream HE1. The PK and tolerability study showed that, when the frequency of application was reduced from daily to twice weekly, the 200 µg/g cream HE1 had good local tolerability.

Therefore, the current study will use these doses compared with vehicle, applied twice weekly on up to approximately 90% BSA in subjects with LI.

7.4. Study Sites

The study will take place at approximately 40 sites in North America, Europe, Israel, and Australia.

7.5. Point of Contact

A point of contact will be identified to provide information to subjects about where to obtain information on the study, the rights of subjects, and whom to contact in case of a study-related injury. This information will be provided in the subject information and ICF.

7.6. End of Study Definition

A clinical study is considered completed when the last participant's last study visit has occurred.

8. SUBJECT POPULATION

8.1. Selection of Study Population and Diagnosis

Diagnosis of LI for the purposes of this study will be a clinical diagnosis. Although some younger subjects may have had genetic testing, older subjects may not.

While LI is a rare disease and subject enrollment may be challenging, due to possible bias introduced by including household members in the same study, it is recommended that only 1 household member be included in the study to maintain the blind and ensure all assessments are independent.

8.2. Study Entry Criteria

8.2.1. Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. Subject is ≥18 years old.
2. Subject has known diagnosis of LI.
3. Subject has moderate to severe (VIIS 3–4) LI on the at least 2 of the 4 body areas assessed (chest/abdomen, back, arms, and legs).
4. Subject has signed an ICF at Screening before any investigational procedures.
5. Subject who is participating in optional photography has signed a photography ICF.
6. Subject who is participating in the optional PK substudy has signed a PK ICF.
7. Subject is not of childbearing potential, i.e., a female who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason, hysterectomy or bilateral oophorectomy),

   OR

- Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception:
  - bilateral tubal ligation
  - combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline
  - hormonal intrauterine device (IUD) inserted at least 1 month before Baseline

  OR

  Agrees to abstain from sex during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study.

  AND

  Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application.

8. Women of child-bearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine).
9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent.
10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

8.2.2. Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization including syndromic ichthyoses.
2. Subject has a history of or current moderate or severe stinging/burning at Screening.
3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments.
4. Subject with a known lipid disorder unless well controlled by stable doses of lipid-lowering agents for at least 6 months.
5. Subject was previously treated with trifarotene/CD5789, including the acne formulation, or participated in previous studies for ichthyosis.
6. Subject has known skeletal disease, hypertriglyceridemia, hypercholesterolemia, liver disease, or other poorly controlled medical conditions.
7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome), Crohn's disease, or any other significant concomitant disease other than LI that, in the investigator's opinion, may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
8. Subject is being treated for major depression disorder.
9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV-positive or to have AIDS at Screening.
10. Subject with any of the following laboratory values at Screening:
    a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory
    b. Triglycerides >200 mg/dL
    c. Total cholesterol >250 mg/dL
    d. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women
    e. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L.
11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
12. Subject has a history of long QT syndrome or clinically significant ECG abnormalities, including clinically significant conduction disorders or significant arrhythmias, QTcF interval >450 ms, PR interval is not between 120 and 220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed.

13. Subject has a known allergy or sensitivity to any of the components of the investigational products.
14. Subject has been exposed to excessive UV radiations on the treated zones within 1 month before Baseline visit or who is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.).
15. Subject is inherently sensitive to sunlight.
16. Subject is presumed to be abusing drug or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms.
17. Subject is participating in another interventional clinical trial.

8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

8.4. Discontinuation of Study Intervention

Discontinuation from study treatment does not mean withdrawal from the study, and the remaining study procedures should be completed as indicated in the study protocol (see Section 10.2.4.5). If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

An investigator may discontinue a participant's study treatment for any of the following reasons:

- Pregnancy
- Significant study intervention noncompliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for discontinuation of study treatment will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized, and receive the study intervention, and subsequently discontinue study treatment, or are withdrawn from the study will not be replaced.

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.5. Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Randomized subjects withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

9.1. Identification of Investigational Products

Trifarotene cream HE1 is a cream containing 100 or 200 µg/g (0.01% [w/w] or 0.02% [w/w], respectively) of CD5789 and the following excipients: purified water, propylene glycol, allantoin, glycerin, medium-chain triglycerides, polypropylene glycol 15 stearyl ether, cyclomethicone, phenoxyethanol, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane (simulgel 600 PHA), sodium benzoate, butylated hydroxytoluene, and gluconolactone.

Vehicle contains the same ingredients, without the CD5789.

Trifarotene cream HE1 and vehicle will be provided in cream form for topical application and will be supplied in 50-g tubes from which a maximum of 36 g of IP may be extracted.

Trifarotene cream HE1 and vehicle will be supplied by G. Production, Inc. (Galderma) in Baie-D'Urfé, QC, Canada.

9.2. Treatments Administered

For the Double-blind Treatment Period, a fixed dose (determined at Visit 2) of trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject.

Study staff will apply the first administration of IP in the clinic on Day 1 after Baseline measurements, and the amount of IP used will be measured (i.e., 50-g tube will be measured before and after application to determine amount used).

The maximum dose per application is 36 g (i.e., 1 tube). Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than full amount of product in a tube.

After the Day 1 visit, subjects will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will continue treatment for up to 12 weeks.

For the OLE Period, all subjects will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the Double-blind Period for an additional 12 weeks.

Subjects should not apply IP on visit days until after the visit.

9.3. Selection of Timing of Dose for Each Subject

Subjects will be randomized in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply approximately the same amount of IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week at least 3 days apart on which to apply their IP (e.g., Tuesday and Friday), and maintain that regimen throughout the study.

All subjects will be provided with diaries in which to record study drug application (days/times) and any areas of skin not treated (e.g., due to local reactions).

If a subject misses an IP application, they should apply the IP as soon as they remember and record the date/time in the subject diary, then wait at least 3 days and continue their regimen.

Subjects should not shower, bathe, or swim for at least 4 hours after IP application. No occlusive dressings should be used on areas to which IP is applied.

Subjects who continue into the Open-label Extension will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the double-blind period for an additional 12 weeks.

9.4. Dose Adjustment Criteria

Local tolerance will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability on a 0–3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) on each of the 4 body areas (chest/abdomen, back, legs, arms), and the following procedures will be followed:

- If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on this area only once weekly, until the score is back to <2;
- If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3.

9.4.1. Stopping Rules

A subject's treatment in either the Double-blind Period or the Open-label Extension must be stopped if any of the following occur:

- Subject becomes pregnant or suspects they are pregnant
- Subject has severe (score of 3) local application site AEs that do not abate with 'drug holiday' and reintroduction of IP.
- Subject has clinically significant changes in laboratory values (liver function tests, cholesterol/triglycerides – which may occur with systemic retinoid use)

9.5. Treatment Compliance

Subjects will be asked to record their twice-weekly applications of IP in the diary during both the Double-blind and OLE Periods. Deviations from the planned doses (missed dose or timing) will be recorded on the subject's eCRF. Study personnel will review diaries at each visit and diaries will be collected as source documents. Information from subject diaries will be transcribed on the appropriate eCRF pages for documentation of subject compliance with the IP.

Study personnel will assess treatment compliance with IP regimens by weighing IP tubes before dispensing and upon return and by questioning the subject, at every post-randomization visit. A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, supplemented by tube weight. A subject who is not compliant (i.e.

used ≤80% or ≥120% of IP tubes) will be counseled at each visit on the importance of using the IP as instructed.

9.6. Method of Assigning Subjects to Treatment Groups

In the double-blind, parallel-group, randomized period of the study, subjects who meet study entry criteria will be randomly assigned in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. Study center will not be a blocking factor in the randomization schedule.

Premier Research will prepare the randomization schedule before the start of the study. No one involved in the study performance will have access to the randomization schedule before the official unblinding of treatment assignments. No subject will be randomized into this study more than once.

In the OLE Period, all subjects will receive trifarotene cream HE1 200 µg/g.

9.7. Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the Double-blind Period of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician and programmer from Premier Research who will have access to the randomization code. The statistician will have access to unblinded data if there is an unblinded DSMB review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will use the IWRS code. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

The primary analysis period is the first 12 weeks of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after database lock has been achieved. A second analysis will take place for endpoints assessed from Week 12 through the OLE Period.

9.8. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

All subjects must washout the following medications after enrollment and before randomization:

Table 9-1: Washout Periods for Prohibited Medications

Medication	Washout Period
Topical Treatments	
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g. tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g. tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	-
Systemic treatments	
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines (except Vitamin D analogues taken at stable dose since at least 1 month)	8 weeks
QT prolonging drugs	5 half lives
Enzymatic inductors (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (not all inclusive: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives

9.8.1. Permitted Therapies

Subjects will be advised on permitted emollient(s) for use on nontreatment days during the study; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited.

Other concomitant medications are allowed (e.g., analgesics, antihistamines), but should be limited to those medications considered necessary. All concomitant medications, both prescribed and over-the-counter, should be recorded in the eCRF.

9.8.2. Prohibited Therapies

The therapies listed in Table 9-1 are prohibited during the study.

Subjects may not use concomitant keratolytics such as urea, salicylic acid, alpha, or beta hydroxyacids. Subjects may not use topical or systemic retinoids. Subjects may not take more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

Subjects receiving excluded therapies will be ineligible for study enrollment or for continued treatment in the study, at the investigator's discretion with consultation with Mayne Pharma LLC and the medical monitor.

9.8.3. Restrictions

Subjects should not shower, bathe, or swim within 4 hours of study drug application. No occlusive dressings should be applied to areas where study drug was applied.

Subjects should only use investigator-approved emollients, and should not use them on treatment days within 4 hours of study drug application.

9.9. Treatment After End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.10. Dispensing and Storage

The test product supplied by Mayne Pharma LLC is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Premier Research. Until the IP is dispensed to the subjects, it must be stored at 20–25°C (68–77°F), with excursions permitted to 15–30°C (59–86°F); do not freeze and with the tube kept tightly closed in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

9.11. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of subjects (subject number) who received the IP. The investigator will not supply the IP to any person except those named as subinvestigators on the Form Food and Drug Administration (FDA) 1572, designated study personnel, and subjects in this study. The investigator will not dispense the IP from any study sites other than those listed on the Form FDA 1572. Investigational product(s) may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Each subject will be given enough tubes of study drug to apply up to 1 tube-full (approximately 36 g of clinical trial material) per treatment day until the next study visit. Tubes will be packed 2 to a carton, and each subject will receive enough cartons to have the maximum number of tubes needed until the next study visit. The number of study drug tubes the subject needs to provide enough IP until the next visit is shown in Table 9-2.

Table 9-2: Amount of Study Drug Needed Per Visit

Treatment Period	Number of Cartons	Number of Tubes
Double-blind Treatment Period		
Baseline	3	6
Day 14	4	8
Day 30	6	12
Day 60	6	12
OLE Period		
Day 90	3	6
Day 104	4	8
Day 120	6	12
Day 150	6	12

Each carton will be weighed before dispensing and subjects are to bring all cartons and tubes back at each study visit, whereupon study staff will weigh them again to estimate study drug use and compliance.

Upon completion of the study, the IP (partly used, unused, and empty tubes) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.12. Labeling and Packaging

Labeling and packaging of IP will be performed by Catalent Pharma Solutions, Philadelphia, PA, USA.

Tubes will be packaged in cartons comprising 2 tubes each. Tubes will be labeled with inner and outer booklet labels, and carton number. Each carton will also be labeled with inner and outer booklet labels and numbered.

9.12.1. Labeling

The tubes will have a label affixed that meets the applicable regulatory requirements and may include, but is not limited to, the following: subject identifier, IP name, lot number, protocol number, carton number, caution statement, storage, and sponsor identification.

Save all empty packaging or packaging containing unused tubes for final disposition by the sponsor or contract pharmacy.

Final labeling will comply with the regulatory requirements of each country where the study will be conducted.

9.12.2. Packaging

Investigational products will be packaged in high-density polyethylene, 35 × 100 mm tubes weighing 50 g from which a maximum of 36 g of IP can be extracted. Trifarotene cream HE1 and vehicle will be packaged so as to be blinded to the investigator, the study clinic personnel, and the subjects.

10. STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

Subjects who agree to participate in the photography and/or PK substudies must provide written informed consent before photographs or serial blood samples are collected.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

10.1.1. Overall Study Schedule

The overall study duration is expected to be approximately 19 months.

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening and Washout: up to 35 days to comprise washout of excluded medications (Table 9-1).
2. Double-blind Treatment: Twice weekly for 12 weeks.
3. Optional Open-label Extension Treatment: Twice weekly for 12 weeks.
4. Follow-up: 14 days after last study drug application.

The maximum treatment duration for each subject is approximately 12 weeks for subjects who choose not to continue into the open-label extension period, and 24 weeks for those who choose to continue.

The maximum study duration for each subject is approximately 229 days (33 weeks).

10.2. Study Periods and Visits

10.2.1. Screening and Washout

10.2.1.1. Screening Visit (Visit 1)

The subject must be screened within 35 days before randomization in the study. The following procedures will be performed at Screening:

1. Obtain written informed consent.
2. Assign a screening number when a subject begins screening.
3. Assess inclusion/exclusion criteria.
4. Collect demographic information.
5. Record medical history, including current therapies (e.g., prescription and nonprescription medications).
6. Perform a physical examination.

7. Measure vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse).
8. Perform a 12-lead ECG.
9. Collect blood and urine for laboratory tests.
10. Perform serum pregnancy test for WOCBP.
11. Record VIIS.
12. Record IGA.
13. Record palm/sole assessment.
14. Record assessment of roughness, and fissuring
15. Record ectropion score.

Procedures for rescreening subjects who initially fail to meet study entry criteria are described in Section 14.3.

10.2.1.2. Washout Period

Excluded medications must be washed over the time periods as shown in Table 9-1. The washout period is part of the 35-day Screening Period.

10.2.2. Double-blind Treatment Period

Eligible subjects who have washed out prohibited medications will be randomized to double-blind study drug.

10.2.2.1. Baseline Visit (Visit 2, Day 1)

The following procedures will be performed on Day 1 in the study clinic:

1. Review inclusion/exclusion criteria.
2. Perform urine pregnancy test for WOCBP.
3. Collect blood and urine for routine laboratory tests (subject must be fasting; i.e., at least 8 hours).
4. Collect a predose PK blood sample (all subjects).
5. Perform physical examination.
6. Record concomitant medications and concomitant therapies.
7. Record VIIS.
8. Record IGA.
9. Record palm/sole assessment.
10. Record assessment of roughness and fissuring.
11. Record ectropion score.
12. Record responses to DLQI and EQ-5D Quality of Life Questionnaires

13. Record vital signs (blood pressure and pulse).
14. Measure and record height, weight, and body mass index (BMI).
15. Perform a 12-lead ECG.
16. Assign randomization number.
17. At sites where the photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
18. Among subjects who consent to participate in the PK substudy, samples will be taken at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1.
19. Clinic staff instructs subject on study drug application, applies initial study drug dose and measures amount used (i.e., study staff will weigh the 50-g tube before and after the first application to determine the fixed dose amount for each subject).
20. Assess and record local tolerance/AEs.
21. Dispense study drug and diaries.
22. Advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.

10.2.2.2. Telephone Visit (Day 7)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.2.3. Visit 3 (Day 14 ±5 days)

The following procedures will be performed on Day 14 in the study clinic:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Assess local tolerance.
4. Record AEs and review diary.
5. Record VIIS.
6. Record IGA.
7. Record palm/sole assessment.
8. Record assessment of roughness and fissuring.
9. Record ectropion score.
10. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.

11. Collect a PK blood sample (all subjects).
12. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
13. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.
14. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.

10.2.2.4. Visit 4 (Day 30 ±7 days)

The following procedures will be performed on Day 30 in the study clinic:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Perform a 12-lead ECG.
4. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
5. Collect a PK blood sample (all subjects).
6. Perform a urine pregnancy test for WOCBP.
7. Record AEs and review diary.
8. Assess local tolerance.
9. Record VIIS.
10. Record IGA.
11. Record palm/sole assessment.
12. Assess roughness and fissuring and record findings.
13. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
14. Record ectropion score.
15. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.
17. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
18. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.

19. Among subjects who consent to participate in the PK substudy, IP will be applied in the clinic at this visit, and samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose.
20. Provide information about OLE option.

10.2.2.5. Telephone Visit (Day 45)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient[s] on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary. Staff will remind subject about OLE option.

10.2.2.6. Visit 5 (Day 60 ±7 days)

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record VIIS.
4. Record IGA.
5. Record palm/sole assessment.
6. Assess roughness and fissuring and record findings.
7. Record ectropion score.
8. Record responses to DLQI and EQ-5D Quality of Life Questionnaires
9. Perform a urine pregnancy test for WOCBP.
10. Collect a PK blood sample (all subjects).
11. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
12. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
13. Record AEs and review diary.
14. Assess local tolerance.
15. Provide information about OLE option.

10.2.2.7. Visit 6 (90 ±7 days) or Early Termination

The following procedures will be performed on Day 90 in the study clinic:

1. Record concomitant medications and concomitant therapies.
2. Perform a physical examination.
3. Record vital signs (blood pressure and pulse).
4. Perform a 12-lead ECG.
5. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
6. Collect a PK blood sample (all subjects).
7. Perform a urine pregnancy test for WOCBP.
8. Record AEs and review diary.
9. Assess local tolerance.
10. Record VIIS.
11. Record IGA.
12. Record palm/sole assessment.
13. Assess roughness and fissuring and record findings.
14. Record ectropion score.
15. Record responses to DLQI and EQ-5D Quality of Life Questionnaires.
16. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
17. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.

For subjects who successfully complete the initial 12 weeks of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing, PK from Day 90/Week 12 will be carried over to the OLE Period and will not be repeated. Subjects will have up to 7 days to decide to enter the OLE; if the subject chooses to continue into OLE, the following additional procedures will be done:

1. Have the subject sign OLE-specific informed consent.
2. Measure subject’s weight.
3. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.
4. Weigh new study drug tubes and dispense enough additional study drug until next visit (only for subjects who choose to continue into the Open-label Extension).

5. Dispense study diary.

10.2.3. Follow-up Telephone Call (±14 days after Day 90) – Only Subjects Who Do Not Continue into Open-label Extension

Clinic staff will telephone subjects who choose not to continue into the Open-label Extension within 14 days after Day 90 to assess any ongoing AEs.

10.2.4. Open-label Extension

Subjects who complete the 12-week Double-blind Treatment Period of the study may choose to continue into an optional 12-week Open-label Treatment Period with trifarotene cream HE1 200 µg/g. During the OLE Period, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and 24 from all subjects who continue into the OLE Period.

10.2.4.1. Telephone Visit (Day 97)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.2. Visit 7 (Week 14; Day 104 ±5 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Assess and record local tolerance/AEs and review diary.
4. Record VIIS.
5. Record IGA.
6. Record palm/sole assessment.
7. Record assessment of roughness and fissuring.
8. Record ectropion score.
9. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
10. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
11. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.

10.2.4.3. Visit 8 (Week 16; Day 120 ±7 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Assess and record local tolerance/AEs and review diary.
4. Record VIIS.
5. Record IGA.
6. Record palm/sole assessment.
7. Record assessment of roughness and fissuring.
8. Record ectropion score.
9. Perform a 12-lead ECG.
10. Collect blood and urine for routine laboratory tests.
11. Perform a urine pregnancy test for WOCBP.
12. Collect a PK blood sample (all subjects).
13. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
14. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
15. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.

10.2.4.4. Telephone Visit (Day 134)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient[s] on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.5. Visit 9 (Week 20; Day 150 ±7 days)

The following procedures will be performed at each study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Perform a urine pregnancy test for WOCBP.

4. Assess and record local tolerance/AEs and review diary.
5. Record VIIS.
6. Record IGA.
7. Record palm/sole assessment.
8. Record assessment of roughness and fissuring.
9. Record ectropion score.
10. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
11. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.

10.2.4.6. Visit 10 (Week 24; Day 180 ±7 days) or Early Termination

The following procedures will be performed at Week 24 in the study clinic:

1. Record concomitant medications and concomitant therapies.
2. Perform a physical examination.
3. Record vital signs (blood pressure and pulse).
4. Perform a 12-lead ECG.
5. Collect blood and urine for routine laboratory tests.
6. Perform a urine pregnancy test for WOCBP.
7. Collect a PK blood sample (all subjects).
8. Assess and record local tolerance.
9. Record AEs and review diary.
10. Record VIIS.
11. Record IGA.
12. Record palm/sole assessment.
13. Assess roughness and fissuring and record findings.
14. Record ectropion score.
15. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.

10.2.4.7. Follow-up Evaluation – Open-Label Period (Week 26/Visit 11)

At 14 days after the last administration of the IP, the following procedures will be performed:

1. Perform a physical examination.
2. Record vital signs (blood pressure and pulse).

3. Record VIIS.
4. Record IGA.
5. Record palm/sole assessment.
6. Assess roughness and fissuring and record findings.
7. Record ectropion score.
8. Perform a urine pregnancy test for WOCBP.
9. Assess and record AEs occurring since the last evaluation and review diary.
10. Record any concomitant medications/therapies.

10.3. Assessments

The VIIS is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. The VIIS scale was developed to generate a reliable method to assess ichthyosis clinical severity using solely scale and erythema, which are the only findings present in ichthyosis of every genetic cause, and occur either upon skin of normal thickness (lamellar subtypes) or upon thickened skin (keratoderma subtypes).[13] The VIIS uses a 5-point index to assess the level of severity of scale and erythema in each of 4 body areas: chest/abdomen, back, legs, and arms, for a possible overall total of 16 points (Section 10.3.1.1). While retinoid treatment is expected to reduce scale, it may increase erythema; therefore, in this study, erythema will be evaluated as part of local tolerability.

10.3.1. Efficacy Variables

All efficacy measurements will use scales previously used for dermatological studies or as defined in the following sections.

10.3.1.1. Visual Index for Ichthyosis Severity – Scaling

The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where “success” is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/EOT on the overall 16-point VIIS for scaling.

The investigator will rate the subject's condition using the 5-point VIIS for each body area (chest/abdomen, back, legs, and arms) and an overall score at each time point shown in the Schedule of Events (Section 2.2):

0	Clear	Normal skin; no perceptible scale or smoothening
1	Almost clear	Areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
2	Mild	Confluent smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
3	Moderate	Confluent scales (visibly separated/fractured stratum corneum) including some large (>1cm), thick scales
4	Severe	Confluent, primarily large, thick scales

10.3.1.2. Investigator's Global Assessment

The IGA will be measured on a 5-point scale.

0	Clear	No scaling and no roughness, no fissure
1	Almost Clear	Occasional fine scales, hardly palpable roughness (mostly smooth), no fissure
2	Mild	Small and fine scales predominate, no more than a few large scales, mild roughness on palpation, few fissures may be present
3	Moderate	Large rather thick scales predominate, coarse roughness on palpation, few fissures may be present
4	Severe	Large coalescent scales dominate, sharp edges on palpation with plate-like hyperkeratosis, many fissures may be present

10.3.1.3. Palm/Sole Assessment

Thickening of the skin on the palms and soles will be measured on a 5-point scale.

0	Clear	No thickening, no roughness, no fissure
1	Almost Clear	Only slight thickening, minimal to no roughness, no fissures
2	Mild	Some thickening, mild roughness on palpation, few fissures may be present
3	Moderate	Substantial and diffuse thickening, coarse roughness on palpation may be present, fissures may be present
4	Severe	Very thickened and rough skin, numerous fissures

10.3.1.4. Individual Score for Roughness

The amount of roughness of the skin overall will be measured on a 5-point scale.

0	Clear	Smooth skin
1	Almost Clear	Hardly palpably roughness
2	Mild	Mild roughness (fine sand paper-like)
3	Moderate	Moderate, coarse roughness (coarse sand paper-like)
4	Severe	Very coarse skin (broken cornflakes-like)

10.3.1.5. Fissuring Assessment

Fissuring will be assessed by recording the presence or absence of fissures, the number of fissures present, and the pain associated with each fissure. The subject will assess pain associated with fissures as ranging from 0–3 (none, mild, moderate, severe).

10.3.1.6. Dermatology Life Quality Index

The DLQI is a dermatology-specific Quality of Life instrument. It is a simple 10-question validated questionnaire with 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment); higher scores indicate poorer quality of life. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology.

10.3.1.7. EQ-5D Quality of Life Questionnaire

The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the subject's self-rated health on a vertical VAS. This can be used as a quantitative measure of health outcome that reflects the subject's own judgement.

10.3.1.8. Ectropion Severity Score

The Ectropion Severity Score (ESS), has a maximum score of 8 points. A higher score indicates a worse ectropion. The score takes the severity of ectropion in terms of lateral and medial apposition, scleral show, conjunctival show, and roundness of the eye into account and gives an indication of the functional aspects involved in ectropion by scoring redness, excess tear film, and the position of the lacrimal punctum.[14]

10.3.2. Clinical Pharmacology

10.3.2.1. Pharmacokinetic Analysis Methods

The pharmacokinetic characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis (NCA).

10.3.2.2. Pharmacokinetic Parameters

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit for trough values.

Subjects who provide written informed consent to participate in the optional PK substudy will provide blood samples for PK analysis predose on Day 1 and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30.

The PK parameter estimates will be completed using WinNonlin (Pharsight Corporation) software using the actual elapsed times from dose administration to sample collection (i.e., not nominal time).

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the maximum concentration (C_{max}) and the time of C_{max} (T_{max}). Additional details of the parameters and their calculation and evaluation will be included in the SAP.

Table 10-1 shows the PK parameters that will be computed for each subject for samples obtained over the planned sampling intervals.

Table 10-1: Pharmacokinetic Parameters

Parameter	Description of Parameter
C_{max}	Maximum (or peak) serum concentration
T_{max}	Time at which C_{max} is observed
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration
$AUC_{(0-inf)}$	Area under the plasma concentration-time curve from time 0 to infinity (if data permit)
$t_{1/2}$	Apparent first order terminal elimination half-life
λ_z	Apparent terminal phase rate constant (if data permit)

10.3.3. Sample Collection

Samples will be collected at the time points specified in the Schedule of Events (Section 2.2). Specimen preparation, handling, shipment, and storage for the complete blood count, chemistry, and urinalysis are described in the study laboratory manual.

Blood

Each blood sample will be 3 mL/kg in volume. The total amount of blood to be drawn for serial PK assessments will be a maximum of 5 mL/kg per subject over a 24-hour period.

Urine

Urinalysis will be performed at central laboratory. Dipstick and urine pregnancy tests will be conducted on site.

10.3.4. Safety Variables

Safety assessments will include the evaluation of AEs, including local tolerability (stinging/burning, pruritus, and erythema), clinical laboratory assessments, vital signs, 12-lead ECGs, and physical examinations.

10.3.4.1. Clinical Laboratory Safety Assessments

10.3.4.1.1. Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 2.2).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides
Coagulation Panel:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones

Pregnancy Test:	for women of childbearing potential only; serum at Screening, urine at each other visit.
Serology	Hepatitis B surface antigen, and hepatitis C

All blood samples for the clinical laboratory tests must be taken in a fasting state, at least 8 hours after the previous drug application.

Blood and urine samples for hematology and serum chemistry will be sent to a central laboratory for analysis. Urine pregnancy tests and dipstick will be conducted at the study sites.

10.3.4.1.2. Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

Samples for assessment of clinical laboratory tests will be transported to Clinical Reference Laboratory (see the study laboratory manual for addresses).

10.3.4.1.3. Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Mayne Pharma LLC prior to beginning the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically significant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical significance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically significant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.4.2. Clinical Examinations

10.3.4.2.1. Vital Signs

Vital signs, including height and weight (only assessed at Screening), blood pressure and pulse will be measured.

10.3.4.2.2. Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. All ECG recordings will be identified with the subject number, date, and time of the recording.

10.3.4.2.3. Physical Examination

A complete physical examination excluding the genitourinary examination will be performed as indicated in the Schedule of Events (Section 2.2).

10.3.4.2.4. Other Safety Variables

Local tolerability will be assessed on a 0–3 scale (none, mild, moderate, severe). All application site reactions will be recorded as AEs.

10.3.4.3. Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Preexisting diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a preexisting condition is considered an AE.)

Events that occur in subjects treated with control product are also considered AEs.

11.1.2. Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADRs).

The phrase “responses to an investigational product” means that a causal relationship between an IP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IP qualify as ADRs.

All AEs for which the judgment of relationship to IP is “possible” or higher will be considered ADRs. If a relationship to IP is not provided, then the AE must be treated as if it were “possible.”

11.1.3. Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For a preapproval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved IP or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events.

11.1.4. Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.5. Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6. Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first application of IP (trifarotene or vehicle) and not more than 14 days after the last application of IP.

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review by a study monitor.

All reported AEs, including local and systemic AEs not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All reported AEs occurring while on study must be documented appropriately regardless of relationship. All reported AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of a reported AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study clinic personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 14 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1. Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs. In addition, although local tolerability will be assessed on a 0-3 scale, all application site reactions should be recorded as AEs.

11.2.2. Evaluation

11.2.2.1. Severity of Adverse Events

The clinical severity of an AE will be classified as follows:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

11.2.2.2. Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3. Action(s) Taken

All AEs will be treated/managed according to standard practice. The following actions may be taken with regard to the IP. Section 9.4 describes dose adjustment and stopping rules for individual subjects.

Action(s) taken may consist of the following:

Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4. Outcome at the Time of Last Observation

The outcome of an AE at the time of last observation will be classified as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5. Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to IP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related	An AE with a reasonable time sequence to administration of the IP, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Related	An AE occurring in a causal plausible time relationship to IP administration that cannot be attributed to a concurrent disease or other drugs, chemicals, or events. The AE relationship to the IP must be assessed separately by the investigator and Mayne Pharma LLC.

11.2.3. Documentation

All AEs that occur within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)

- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IPs

11.2.4. Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject may be withdrawn for treatment but continue to be followed for efficacy and safety in the study. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

It is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5. Follow-up

Any AE will be followed (up to a maximum of 14 days after the last dose of IP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6. Reporting

11.2.6.1. Serious Adverse Events

The investigator or designee must report all SAEs promptly to Premier Research within 24 hours of first becoming aware of the event by e.g., completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the Premier Research by one of the following methods:

Email: globalPV-US@premier-research.com

Email: PVDS-ROW@premier-research.com

Fax number: +1 215 972 8765

Fax number: +421 2 6820 3713

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of IPs
- Date of last dose of IPs, if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IPs ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, adverse event, date of occurrence, subject identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the Premier Research Pharmacovigilance Department using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB)/independent ethics committee (IEC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.2. Adverse Drug Reactions

All ADRs should be reported by the investigator in the eCRF.

Suspected serious ADRs must be reported to the sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.3. Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported by Premier Research to Mayne Pharma LLC in aggregate monthly status reports.

11.3. Special Considerations

11.3.1. Adverse Events of Special Interest

Since topical retinoids are associated with local application site AEs, particularly when beginning treatment, these events will be followed closely during the study and considered AEs of special interest (AESIs).

11.3.2. Pregnancy

All WOCBP who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during IP treatment will be immediately discontinued from study treatment. The investigator must report the pregnancy of any woman who becomes pregnant during or within 30 days after discontinuing treatment as if it were an SAE within 24 hours of learning of the pregnancy, to Premier Research Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an SAE and AE form (entering the event temporarily as nonserious on both forms) provided by the sponsor or its designee. If a partner of a male study subject becomes pregnant, the investigator must report the pregnancy as soon as possible after learning of it to the Premier Research Pharmacovigilance using the Pregnancy Data Collection Form. A separate pregnant partner ICF will be required.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy in a study subject. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

12. DATA SAFETY MONITORING BOARD

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including LI. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate under a charter that will be finalized prior to the start of the study. The DSMB will meet at least 3 times during the conduct of the study: when the study begins, when 15 subjects have enrolled in Cohort A and have completed at least 28 days of treatment, and after 60 subjects have enrolled in the study.

The DSMB will meet after subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data. The data will remain blinded unless an issue or trend arises that requires unblinding. At that time, the DSMB will decide whether Cohort B may begin enrolling. The DSMB will have the authority to recommend to the sponsor that the study be placed on hold or discontinued if serious safety issues are discovered. The DSMB will provide its input to Mayne Pharma LLC.

In case of significant toxicity, the DSMB may choose to review the available safety data and recommend stopping recruitment in a particular dose group. If toxicity is observed, the treatment assignment for the subject(s) involved may be unblinded by the DSMB at its discretion.

Stopping rules for individual subjects are in Section 9.4.1.

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. An SAP that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a *P* value of ≤ 0.05 will be considered statistically significant.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will include the number and percentage of subjects in each category.

The primary analysis period is the first 12 weeks of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after the database is locked. A second analysis will take place for endpoints assessed from Week 12 through the OLE Period. The baseline for the safety and efficacy parameters will be measured at Visit 1 or Visit 2, per the Schedule of Events for both the Double-blind (Table 2-1) and OLE (Table 2-2) Periods.

13.1.1. Analysis Populations

The following 5 analysis populations are planned for the Double-blind Period of this study:

- Safety: all subjects who are randomized to treatment and receive at least 1 application of study drug in the Double-blind Period. This population will be the primary population for analyses of safety.
- Intent-to-treat (ITT): all randomized subjects.
- Modified intent-to-treat (mITT): all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period.
- Per-protocol (PP): subjects in the mITT Population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations.
- Pharmacokinetic: all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. This population will be used to summarize all PK endpoints.

The following analysis populations are planned for the OLE Period of this study:

- OLE Safety: all subjects who complete the 12-week Double-blind Treatment Period and receive at least 1 application of study drug in the OLE Period.
- OLE ITT: all subjects who complete the 12-week Double-blind Treatment Period and sign the OLE informed consent.
- OLE mITT: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6.

- OLE PP: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study.

Inclusion in the analysis populations will be determined prior to database lock.

If a subject is randomized incorrectly or is administered the incorrect IP, analyses of the ITT and mITT populations will be based on the assigned treatment whereas all other analyses will be based on the actual treatment received.

13.1.2. Study Subjects and Demographics

13.1.2.1. Disposition and Withdrawals

For the Double-blind Period, the numbers of subjects randomized, completing Week 12 of the study, and withdrawing early from the Double-blind Period, along with reasons for withdrawal, will be tabulated overall and by randomized treatment group. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated by randomized treatment group. This analysis will be conducted for the ITT population.

For the OLE Period, the number of subjects entering the OLE Period, completing the study, and withdrawing early, along with reasons for withdrawal, will be tabulated overall. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated. This analysis will be conducted for the OLE ITT population.

13.1.2.2. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations promptly. All deviations must be addressed in study source documents, and reported to Premier Research or Mayne Pharma LLC. Protocol deviations must be sent to the reviewing IRB/IEC per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB/IEC requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

13.1.2.3. Demographics and Other Baseline Characteristics

These analyses will be conducted for the ITT and OLE ITT populations.

Demographic variables will include age, sex, race, ethnicity, height, weight, and BMI. Baseline subject characteristics will include medical history, physical examination findings, and VIIS score.

Prior and concomitant medications will be summarized by randomized treatment group, by the number and percentage of subjects taking each medication, and classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.1.3. Exposure and Compliance

Investigational product administration will be summarized in terms of each subject's dose, and in terms of duration of exposure for each period. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group. Additionally, the number of subjects who are compliant with investigational product will be presented by treatment group for the Double-blind Period and overall for the OLE.

13.1.4. Efficacy Analysis

The mITT population will be used as the primary population for the primary analysis of efficacy at Week 12. All efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE Period using the OLE mITT and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE Period.

13.1.4.1. Efficacy Endpoints

Primary efficacy endpoint: The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/ EOT in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0-4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs).

Secondary: The secondary endpoints are as follow:

- The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices:
  - IGA (Scale: 0-4) for each body area
  - Palm/sole Assessment (Scale: 0–4)
  - Individual score for roughness (Scale: 0–4) overall
- The difference in proportion of subjects with presence of fissures (presence/absence, number of fissures, and pain associated with fissures [on a 0-3 scale]) between the active trifarotene cream HE1 and vehicle groups
- Quality of life per Dermatology Life Quality Index (DLQI)

Exploratory: The exploratory endpoints are as follow:

- The difference in mean ectropion scores (ESS of 0–8) between the active trifarotene cream HE1 and vehicle groups
- Quality of life per EQ-5D-5L

13.1.4.2. Primary Analysis

For the Double-blind Period only, the number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT will be presented along with the difference in proportions between each trifarotene cream HE1 group and vehicle. 95% confidence intervals (CI) will be provided for proportions. Generalized estimating equations (GEE) for binary response will be used to model the odds of successful resolution of LI with treatment group as a predictor. Other covariates, such as baseline VIIS scores, baseline characteristics, and interactions may be included. Various correlation matrix structures will be explored to model the within subject correlation. Additionally, the difference in mean VIIS score at Week 12/EOT between the active trifarotene cream HE1 groups and vehicle group will be analyzed using a 2-sided, 2-sample Wilcoxon rank-sum test at the 5% significance level. The null hypothesis is that the mean of each trifarotene cream HE1 group is equal to the mean of the vehicle group.

Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from Baseline will be provided for VIIS scores for both periods.

13.1.4.3. Secondary Analyses

Secondary and exploratory efficacy endpoints will be analyzed separately for each period (Double-blind and OLE) using descriptive statistics.

Additionally, for the Double-blind Period only, change from Baseline through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate. Frequencies of results and 95% CIs will also be reported, and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test.

For subjects who report having fissures, descriptive summaries of the number of fissures and pain related to fissures will also be presented by treatment group and body area for each period.

The DLQI scores will also be analyzed using descriptive statistics through Week 12.

13.1.4.4. Exploratory Analyses

Descriptive summaries and the changes from Baseline will be provided for ectropion scores and EQ-5D-5L scores by visit for each period. No formal inferential analyses will be conducted for exploratory endpoints.

13.1.4.5. Corroborative, Sensitivity, and Other Analyses

To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using LOCF for the Double-blind Period only. Imputation will not be performed in the OLE period.

For analyses involving study site, if the number of subjects per site is small, sites may be pooled for safety and efficacy analysis or omitted from statistical models as the anticipated number of subjects per site is small, treatment is self-administered, and the sites are using standardized procedures for all assessments. If the distribution of enrollments at sites is such that one or few are

enrolling a majority of subjects, a subgroup analysis by site may be performed. The final determination will be made prior to database lock.

Details of these analyses will be further detailed in the SAP.

13.1.5. Clinical Pharmacology Analyses

13.1.5.1. Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics. Descriptive statistics reported will include the arithmetic mean, SD, CV%, geometric mean, minimum, maximum, and median. Only the range and the median will be reported for T_{max}, as this is a categorical parameter. The PK parameters will also be summarized by treatment using descriptive statistics.

Individual plasma concentration plots and mean data graphs will be produced using both linear and semi-logarithmic scales. Mean data graphs will show plasma concentration profiles by treatment group.

Pharmacokinetic plasma parameter estimates and summaries will be completed for the subjects in the PK population. Testing of PK parameters will be outlined in the SAP.

13.1.6. Safety and Tolerability Analyses

Safety analyses through Week 12 of the Double-blind Period will be conducted using data from the Safety Population and safety analyses in the OLE Period will be conducted using the OLE Safety Population (as defined in Section 13.1.1). Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, and physical examination results. No formal inferential analyses will be conducted for safety variables in either period.

13.1.6.1. Local Tolerability

During all clinic visits, the investigator will assess local tolerability (Scale: 0–3 [none, mild, moderate, severe]) on each of the 4 body areas (chest/abdomen, back, legs, arms). Descriptive summaries will be presented by period, treatment group, and visit.

13.1.6.2. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1 or higher.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first, or
- AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first.

The number and percentage of subjects with AEs will be displayed by each treatment group in the Double-blind Period and overall in the OLE by system organ class and preferred term. Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.6.3. Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each treatment group at each time point in each period.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from Baseline (shift tables) for each clinical laboratory parameter by treatment group and by study visit in each period.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.1.6.4. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse for each period.

The number of subjects with vital signs values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each parameter by period, by treatment group and by study visit. Pre- and post-treatment values may also be presented with an analysis of mean changes from Baseline.

13.1.6.5. Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point in each period. Abnormal results will be grouped as clinically significant and not clinically significant.

A comparison of QT results will be presented. Summary statistics will be displayed by period, by treatment group, and by visit for QT and the QT interval corrected for heart rate (QTc) calculated using Fridericia's QT correction methods.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTcF interval (Fredericia's correction methods), and HR for each treatment group at each time point in each period.

13.1.6.6. Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group in each period.

13.1.7. Interim Analysis

No interim analyses are planned.

13.2. Sample Size Determination

Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) using a 2-sample t-test assuming a mean difference of at least 1.0 and a standard deviation of 1.4 or lower. This study is not powered to detect a difference between the 2 active arms.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1. Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6 for US studies/Section 14.6.1 for studies conducted outside of the US).

Mayne Pharma LLC agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2. Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with ICH GCP, and the applicable United States (US) Code of Federal Regulations (CFR). The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the IRB/IEC, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IPs, and their specific duties within the context of the study. Investigators are responsible for providing Mayne Pharma LLC with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Premier Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Premier Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Premier Research

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory/GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening Visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4. Study Documents

All documentation and material provided by Mayne Pharma LLC for this study are to be retained in a secure location and treated as confidential material.

14.4.1. Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The informed consent forms are submitted with this protocol.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB/IEC-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent forms and ask questions before signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2. Investigator's Regulatory/Good Clinical Practice Documents

The regulatory/GCP documents are listed below.

- Signed original protocol (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and subinvestigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form Signature Log/Delegation of Study-related Duties
- Approved ICF and subject materials
- FDA1572 and financial disclosure forms, as applicable (US sites)
- Any other relevant GCP documents

The regulatory/GCP documents must be received from the investigator and reviewed and approved by Mayne Pharma LLC or its designee before the study site can initiate the study and before Mayne Pharma LLC will authorize shipment of IP to the study site. Copies of the investigator's regulatory/GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the trifarotene (CD5789) Cream IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and IP accountability records should also be retained as part of the investigator's regulatory/GCP documents. It is the investigator's responsibility to ensure that

copies of all required regulatory/GCP documents are organized, current, and available for inspection.

14.4.3. Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4. Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.5. Data Quality Control

Mayne Pharma LLC and its designees will perform quality control checks on this clinical study.

14.5.1. Monitoring Procedures

Mayne Pharma LLC and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Mayne Pharma LLC personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures

- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF will be provided to the sites. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Mayne Pharma LLC or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan (CMP).

14.5.2. Data Management

Mayne Pharma LLC or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data management plan (DMP) will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries will be provided to the sites.

14.5.3. Quality Assurance/Audit

This study will be subject to audit by Mayne Pharma LLC or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or clinical study report [CSR])

Mayne Pharma LLC or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Mayne Pharma LLC immediately.

14.6. Study Termination

The study may be terminated at Mayne Pharma LLC's discretion at any time and for any reason.

The DSMB may recommend discontinuation of the study if they find evidence of unacceptable risk to subjects.

14.6.1. Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, Mayne Pharma LLC or designee will notify the IECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

14.6.2. Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by Mayne Pharma LLC, IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Mayne Pharma LLC or its designee will notify the IECs and regulatory authorities about the premature termination as required according to national laws and regulations. Mayne Pharma LLC or its designee must clearly explain the reasons for premature termination.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the IND or IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is terminated prematurely, all investigators have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Follow-up Visit.

The study might resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or FDA.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. Mayne Pharma LLC may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1. Record Retention

For sites in the US, the investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until 1 of the following occurs:

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

Outside of the US, after completing the study, Mayne Pharma LLC will receive the original eCRFs or at least a legible copy and retain the documents for at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

14.7.2. Sample Retention

Blood samples will be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

Data collected for this study will be analyzed and stored at Premier Research.

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Mayne Pharma LLC. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9. Use of Information and Publication

All information concerning trifarotene (CD5789) cream HE1, Mayne Pharma LLC's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Mayne Pharma LLC or its designee to the investigator, and not previously published, is considered confidential and remains the sole property of Mayne Pharma LLC. Case report forms also remain the property of Mayne Pharma LLC. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by Mayne Pharma LLC in connection with the continued development of trifarotene (CD5789) cream HE1 and thus, may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Mayne Pharma LLC. Publication or other public presentation of trifarotene (CD5789) cream HE1 data resulting from this study requires prior review and written approval of Mayne Pharma LLC. Abstracts, manuscripts, and presentation materials should be provided to Mayne Pharma LLC for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until Mayne Pharma LLC has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov and clinicaltrialsregister.eu, and results information from this study will be submitted.

15. FINAL CLINICAL STUDY REPORT

Mayne Pharma LLC will retain ownership of the data.

The final CSR will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

16.2. Subject Information and Informed Consent

A properly constituted, valid IRB or IEC must review and approve the protocol, the investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed consent prior to enrollment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Mayne Pharma LLC, and/or the sponsor's designee. Collection of informed consent has to be documented in the eCRF.

Furthermore, the subject will be informed that if he or she wishes to dropout or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

16.3. Approval by Institutional Review Board and Independent Ethics Committee

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's or the sponsor's representative before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must follow local country requirements.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by Mayne Pharma LLC before implementation.

16.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

17. REFERENCES

1. Vahlquist A, Blockhuys S, Steijlen P, et al. Oral liarozole in the treatment of patients with moderate/severe lamellar ichthyosis: results of a randomized, double-blind, multinational, placebo-controlled phase II/III trial. *Br J Derm*. 2014;170(1):173-181.
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3. Vahlquist A, Gånemo A, Virtanen M. Congenital ichthyosis: an overview of current and emerging therapies. *Acta Derm Venereol.* 2008;88(1):4–14.
4. Blanchet-Bardon C, Nazzaro V, Rognin C, Geiger JM, Puissant A. Acitretin in the treatment of severe disorders of keratinization. *J Am Acad Dermatol.* 1991;24(6):982–986.
5. Kullavanijaya P and Kulthanan K. Clinical efficacy and side effects of acitretin on the disorders of keratinization: a one-year study. *J Dermatol.* 1993;20:501–506.
6. Lacour M, Nikhar-Mehta B, Atherton DJ, Harper JI. An appraisal of acitretin therapy in children with inherited disorders of keratinization. *Br J Dermatol.* 1996;134:1023–1029.
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12. Chiaretti A, Wismayer DS, Tortorolo L, Piastra M, Polidori G. Salicylate intoxication using a skin ointment. *Acta Paediatr*. 1997;86(3):330–331.
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14. Korteweg SFS, Stenekes MW, van Zyl FE, Werker PMN. Paralytic Ectropion treatment with lateral periosteal flap canthoplasty and introduction of the ectropion severity score. *Plast Reconstr Surg Glob Open*. 2014;2(5):e151.

18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER:	18-ICH-001
PROTOCOL TITLE:	A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
FINAL PROTOCOL DATE:	v2.0 for Ukraine, 21-Oct-2019

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Mayne Pharma LLC and Premier Research during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical studies on an IP during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

PROTOCOL NUMBER:	18-ICH-001
PROTOCOL TITLE:	A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Subjects with Autosomal Recessive Ichthyosis with Lamellar Scale
FINAL PROTOCOL DATE:	v2.0 for Ukraine, 21-Oct-2019

The undersigned acknowledges possession of and has read the product information (e.g., the IB) on the IP and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected subjects in his/her care, according to the study protocol.

He or she agrees to use the study material, including IP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Mayne Pharma LLC.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Mayne Pharma LLC within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IP.

He or she agrees to comply with Mayne Pharma LLC and regulatory requirements for the monitoring and auditing of this study.

In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

APPENDICES

A. Regulations and Good Clinical Practice Guidelines

A. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives (and applicable regulations/guidances):

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents>

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

PROTOCOL/CLINICAL INVESTIGATION PLAN AMENDMENT

PRODUCT NAME/NUMBER:	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER:	18-ICH-001
IND NUMBER:	140538
NCT NUMBER:	NCT03738800
EUDRACT NUMBER:	2018-003272-12
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale
PROTOCOL DATE:	Original: 28-Nov-2018; Version 2.0: 10-Jul-2019
AMENDMENT 1 DATE:	Final, 10-Jul-2019
COORDINATING/PRINCIPAL INVESTIGATOR:	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine, PO Box 208059 333 Cedar Street New Haven, CT 06520, USA +1 203 789 1249
SPONSORED BY:	Mayne Pharma LLC 1240 Sugg Parkway Greenville, NC 27834, USA +1 984 242 1400
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive, Suite 150 Durham, NC 27709, USA +1 919 627 9100

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: 18-ICH-001

PROTOCOL TITLE: A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale

I, the undersigned, have read this protocol and confirm that to the best of my knowledge, it accurately describes the planned conduct of the study.

SIGNATURE **DATE:**

DocuSigned by:
Ilana Stancovski
Signer Name: Ilana Stancovski
Signing Reason: I approve this document
Signing Time: 16-Jul-2019 | 10:49 EDT
ED06BBBB3AE5401189B961E2C5050B77

16-Jul-2019 | 10:49:28 EDT

Ilana Stancovski, PhD
Chief Scientific Officer
Mayne Pharma LLC

DocuSigned by:
Phoevos Hughes
Signer Name: Phoevos Hughes
Signing Reason: I approve this document
Signing Time: 16-Jul-2019 | 11:48 EDT
2D1DC1CA65A8487 18371307AF875E4CE

16-Jul-2019 | 08:49:00 PDT

Phoevos Hughes, JD
Associate Director, Clinical Operations
Mayne Pharma LLC

DocuSigned by:
Marlis Sarkany
Signer Name: Marlis Sarkany
Signing Reason: I have reviewed this document
Signing Time: 17-Jul-2019 | 07:51 EDT
16E1C8AEDC854CDC86688C1FD466E26F

17-Jul-2019 | 07:53:06 EDT

Marlis Sarkany, MD
Senior Medical Director
Premier Research

DocuSigned by:
Adrienne Kuxhausen
Signer Name: Adrienne Kuxhausen
Signing Reason: I approve this document
Signing Time: 17-Jul-2019 | 08:44 EDT
6E6B87C6B98740819F26B8D5A7D662CF

17-Jul-2019 | 08:44:28 EDT

Adrienne Kuxhausen, MS
Senior Biostatistician
Premier Research

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER	18-ICH-001
EUDRACT NUMBER	2018-003272-12
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, and Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale
INDICATION	Lamellar ichthyosis
OBJECTIVES	Primary: To compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in adults and adolescents with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 12 weeks of treatment. Secondary: • To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% body surface area (BSA) twice weekly. • To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.
STUDY DESIGN	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Investigator's Global Assessment [IGA] where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe). Adults (Cohort A) and adults and adolescents (Cohort B) will be randomized in a double-blind fashion to 1 of 2 doses of trifarotene cream HE1 or vehicle and treated twice weekly for 12 weeks. Subjects who complete the randomized, Double-blind Period of the study will be eligible to enter a 12-week, Open-label Extension (OLE) in which additional PK, safety, and efficacy data will be collected. Approximately 15 adults (≥18 years old) will be randomized into the first cohort of subjects (Cohort A) in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks. After the initial 15 subjects complete at least 28 days of treatment, an independent data safety monitoring board (DSMB) will review aggregate safety and tolerability data (including PK and electrocardiogram [ECG] data). If no safety issues are identified, both adults and adolescents (ages 12 to 17 years, inclusive) will be allowed to enroll in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks in the same manner as subjects in Cohort A. All subjects (Cohort A and Cohort B) who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for up to 12 weeks. Written informed consent will be obtained from a parent/legal guardian for any minor and minors will provide assent before any study-related procedures are performed.

Upon signing informed consent and entering the Screening Period, subjects may begin washout, during which they will stop using physical and medical treatments for LI, including balneotherapy and the following prohibited medications, as applicable. Washout may be up to 3 months, as necessary.

a. Topical treatments

Medication	Washout
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	2 weeks

b. Systemic treatments

Medication	Washout
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines (except Vitamin D analogues taken at stable dose since at least 1 month)	8 weeks
QT prolonging drugs	5 half lives
Enzymatic inductors (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (not all inclusive: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives
Monoclonal antibody treatment (e.g., anti-IL17)	5 half lives

During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower but not bathe or swim during the Screening Period.

After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.

Study drug will be packaged in 50-g tubes from which up to 36 g of investigational product (IP) may be dispensed per application, i.e., the maximum dose per application. Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied. If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.

Thereafter, each subject will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the

	full amount of product in a tube. Subjects will record the date and time of study treatment administration in the subject diary. Local tolerability may differ in subjects with LI compared to healthy subjects, as their skin is drier and may be more sensitive. Local tolerability will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45 in the Double-blind Period; at Day 97 and 134 in the OLE) to assess safety; an unscheduled clinic visit may be performed, if necessary. If the treatment causes application site reactions, the frequency of application will be reduced or interrupted only on the area of concern, as indicated herein. During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for stinging/burning, pruritus, erythema) for each body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed: - If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas. - If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas. Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and adverse events (AEs). Any changes in dosing must be documented in the subject diary and the electronic case report form. All subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]) and any AEs, including application site reactions and concomitant medications used. Subjects will also be advised on permitted emollient(s) use on nontreatment days during the study; use of emollient(s) and/or sunscreen(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. At all sites with photographic capability, photographs will be taken as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional photographic informed consent form (ICF). Samples for pharmacokinetic (PK) analysis will be drawn from all subjects at Baseline and at each clinic visit. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained on the skin after the last application. Subjects should not apply IP on visit days until after the visit. In addition, a PK substudy will be conducted on Days 1 and 30 at sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 30 subjects, 15 adults and 15 adolescents. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for these subjects at each of the other clinic visits. For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30. Subjects who complete the Double-blind Treatment Period will have the option to continue into the OLE to assess safety for an additional 12-weeks with trifarotene cream

	HE1 200 µg/g twice weekly, on up to 90% of BSA, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. During the OLE, subjects will return to the site at Weeks 14, 16, 20, 24, and 26 for safety, tolerability, and efficacy assessments. Blood samples will be drawn for clinical laboratory safety tests and PK at Weeks 16 and 24. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 97 and Day 134) to assess safety; an unscheduled clinic visit may be performed, if necessary.
PLANNED NUMBER OF SUBJECTS	Approximately 120 total subjects; 15 adult subjects in Cohort A and 105 adult and adolescent subjects in Cohort B.
STUDY ENTRY CRITERIA	Inclusion criteria: 1. For Cohort A: subject is ≥18 years old; for Cohort B: subject is ≥12 years old. 2. Subject has known diagnosis of LI. 3. Subject has moderate to severe (IGA 3-4) LI on the IGA of LI severity. 4. Subject has signed an ICF at Screening before any investigational procedures. Subjects <18 years of age (or Age of Majority) must sign an assent form in conjunction with an ICF signed by the parent/legal representative. 5. Subject who is participating in photography has signed a photography ICF. 6. Subject who is participating in the optional PK substudy has signed a PK ICF. 7. Subject is not of childbearing potential, i.e., a female who has not yet begun menstruating or who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason, hysterectomy or bilateral oophorectomy), OR Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception: • bilateral tubal ligation • combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline OR Agrees to abstain from heterosexual intercourse during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. AND Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application. Note: Subjects who are premenstrual at Screening but begin menses during the study should follow the pregnancy testing schedule for WOCBP and must abstain from

	sexual intercourse while in the study and for at least 1 month after the last study drug application. 8. Women of child-bearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine). 9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent/assent, as applicable. 10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin). Exclusion criteria: 1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization, including syndromic ichthyoses. 2. Subject has current moderate or severe stinging/burning at Screening. 3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments. 4. Subject with a known lipid disorder (hypertriglyceridemia >200 mg/dL, hypercholesterolemia >250 mg/dL) unless well controlled by stable doses of lipid-lowering agents for at least 6 months. 5. Subject was previously treated with trifarotene/CD5789 in an acne or ichthyosis study. 6. Subject has any other significant concomitant disease, or poorly controlled medical condition other than LI that in the investigator's opinion may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments.. 7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis). 8. Subject is being treated for major depression disorder and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts. 9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening. 10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory b. Total bilirubin >1.1 mg/dL or, in case of Gilbert's syndrome, total bilirubin >3 mg/dL c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women d. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L 11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 12. Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment. 13. Subject has a history of long QT syndrome or clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, QTcF interval >450 ms, PR interval is not between 120 and

	220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed. 14. Subject has a known allergy or sensitivity to any of the components of the investigational products. 15. Subject has been exposed to excessive ultraviolet (UV) radiations on the treated zones within 1 month before Baseline visit or is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.). 16. Subject is inherently sensitive to sunlight. 17. Subject is unable or unwilling to stop use of topical or systemic retinoids. 18. Subject is presumed to be abusing drugs or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms. 19. Subject is participating in another interventional clinical trial. 20. Subject is institutionalized. 21. Subject is in any way related to the sponsor, investigator, or site personnel.
INVESTIGATIONAL PRODUCT	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Extension dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 200 µg/g applied topically twice weekly on up to 90% BSA
REFERENCE PRODUCT(S)	Name: Vehicle cream Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) applied topically twice weekly on up to 90% BSA
TREATMENT REGIMENS	Topical application twice weekly to all affected skin except the scalp, axillae, and inguinal area.
COORDINATING/ PRINCIPAL INVESTIGATOR	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine New Haven, CT 06520, USA
PLANNED STUDY SITES	Approximately 40 sites across North America, Europe, Israel, and Australia

CRITERIA FOR EVALUATION	Primary efficacy endpoint: The proportion of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear on treated areas and at least a 2-grade change from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA full body scale.
	
	Secondary endpoints:
	
	– The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Week 12:
	  – 5-point Visual Index for Ichthyosis Severity (VIIS) for scaling from Baseline through Week 12 (overall 16 points for scaling, i.e. 0-4 points for 4 body areas: chest/abdomen, back, arms and legs)
	  – Individual score for roughness (Scale: 0–4) overall
	  – Palm/sole Assessment (Scale: 0–4)
	  – Quality of life per Dermatology Life Quality Index (DLQI) and children's DLQI (cDLQI)
	– The difference in proportion of subjects with presence of fissures on palms/soles (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) at Week 12 between the active trifarotene cream HE1 and vehicle groups
	
	Exploratory endpoints:
	
	– The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12
	– The difference in quality of life per EQ-5D-5L and EQ-5D-Y score between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12
	
	Safety endpoints:
	
	– Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs
	– Local tolerability (Scale: 0-3 [none, mild, moderate, severe], determined by the investigator) for each body area (chest/abdomen, back, legs, arms, and face/neck).
	
	Pharmacokinetic endpoints: Plasma concentrations of CD5789 and its major metabolites will be measured.

STATISTICAL METHODS	Analysis Populations: The following are planned for the Double-blind Period of the study: The Safety population will be the primary population for analyses of safety and tolerability and will comprise all subjects who are randomized to treatment and receive at least 1 application of study drug. The intent-to-treat (ITT) population will comprise all randomized subjects. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The modified intent-to-treat (mITT) population comprises all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The per protocol (PP) population will be defined prior to database lock and will comprise subjects in the mITT population who met all inclusion criteria and no exclusion criteria,

	were compliant with study drug application, and who had no significant protocol deviations. The PK population includes all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. The PK population will be used to summarize all PK endpoints. The following populations are planned for the OLE of this study: The OLE Safety population: all subjects who complete the 12-week Double-blind Treatment Period and receive at least 1 application of study drug in the OLE. OLE ITT population: all subjects who complete the 12-week Double-blind Period and who sign the OLE informed consent. The OLE mITT population: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6. The OLE PP population: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study. Subject Characteristics and Disposition: Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and baseline characteristics for all enrolled subjects. Medical history, physical examination findings, and vital sign measurements for all randomized subjects will be presented in listings. Efficacy Analyses: The number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT in the Double-blind Period will be presented. The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream groups, 95% CIs for the differences, and P-values for the differences in treatment will also be presented. The IGA scores as well as secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Week 24. Change from Baseline through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from Baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and Baseline score value as a covariate. Frequencies of results and 95% confidence intervals will also be reported, and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test. For subjects who report having fissures, the number of fissures and pain related to fissures will also be presented on a scale of 0-3 (none, mild, moderate, severe). Clinical Pharmacology Analyses: Noncompartmental PK analysis will be performed for the PK subset of subjects, as data permit. Plasma concentrations of CD5789 and its major metabolites will be measured and will be listed by subject. Safety Analyses: Safety and tolerability will be assessed based on the incidence of reported TEAEs, and SAEs, including relationship to study drug and severity, as well as physical examination findings, vital sign measurements (supine systolic blood pressure [SBP] and diastolic blood pressure [DBP] and pulse), clinical laboratory results (hematology, including serum aminotransferases and serum lipids, coagulation, clinical chemistry, and urinalysis) and 12-lead ECGs. Descriptive statistics for observed values and change from Baseline will be calculated at each visit within each study period and by treatment group within cohort.

SAMPLE SIZE DETERMINATION	The first cohort of 15 adult subjects is a reasonable sample size to assess safety and tolerability before enrolling adolescents. Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively.. This study is not powered to detect a difference between the 2 active arms.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study will be as follows: 1. Screening: Up to 35 days (after signing informed consent, if necessary, washout may be up to 3 months, and subjects should return to the site after washout to complete the study eligibility requirements). 2. Double-blind study drug application: Twice weekly for up to 12 weeks. 3. Optional Open-label Extension: Twice weekly for up to 12 weeks. 4. Follow-up: 14 days after last study drug application. The maximum study duration for each subject is approximately 229 days (33 weeks). The maximum treatment duration for each subject is 24 weeks.

2.2. Schedule of Events

Table 2-1: Schedule of Events for Double-blind Period

	Screening (-35 days to -1 day) Washout up to 3 months[a]	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[b,c] ± 7 days (ET)
Visit	**1**	**2**		**3**	**4**		**5**	**6**
Week		**1**		**2**	**4**		**8**	**12**
Written informed consent/assent	X							X[a]
Assign screening number	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical history	X							
Physical examination	X	X[d]						X[c]
Vital signs (blood pressure and pulse)	X	X		X	X		X	X
Height, weight, and BMI	X							X
IGA assessment[e]	X	X		X	X		X	X
VIIS[f] assessment	X	X		X	X		X	X
Roughness assessment[g]	X	X		X	X		X	X
Palm/sole assessment	X	X		X	X		X	X
Palm/sole fissuring assessment[h]	X	X		X	X		X	X
Ectropion score	X	X		X	X		X	X
Photographs[i]		X			X			X
Quality of life per Dermatology Life Quality Index (DLQI)		X		X	X		X	X

	Screening (-35 days to -1 day) Washout up to 3 months[a]	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[b,c] ± 7 days (ET)
Visit	**1**	**2**		**3**	**4**		**5**	**6**
Week		**1**		**2**	**4**		**8**	**12**
EQ-5D Quality of Life Questionnaire		X		X	X		X	X
12-lead ECG[j]	X	X			X			X
Clinical laboratory tests (hematology, chemistry, urinalysis)[k]	X	X			X			X
Serology (hepatitis B surface antigen, hepatitis C)	X							
Pregnancy test for female subjects (serum at Screening; urine subsequently)[l]	X	X			X		X	X
Randomization via IWRS		X						
PK blood sample collection[m]		X		X	X		X	X
Initial study drug application by clinic staff and measurement[n]		X						
Application instructions, advice on emollient and sunscreen use		X	X	X	X	X		
Dispense study drug and diaries[o]		X[p]		X	X		X	
Concomitant medications	X	X	X	X	X	X	X	X
Tolerability assessment		X		X	X		X	X
Adverse events (and review diaries)		X	X	X	X	X	X	X
Collect all used/unused study drug[q]				X	X		X	X
Provide information about OLE option					X	X	X	

Abbreviations: BMI = body mass index; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears,

nose, throat; ICF = informed consent form; IGA = Investigator's Global Assessment; IWRS = interactive web response system; OLE = open-label extension; PK = pharmacokinetic; WOCBP = women of childbearing potential; VIIS = Visual Index for Ichthyosis Severity

a. Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods, as applicable. Washout may be up to 3 months, as necessary. During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower but not bathe or swim during the Screening Period. After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.
b. Day 90 procedures should be conducted for subjects who terminate the study early. If a subject discontinues IP, but continues to attend clinic visits, Day 90 will occur as scheduled. Day 90/Week 12 will be the first visit of the OLE for subjects who choose to continue (subjects will have up to 7 days to decide to sign the ICF and begin the OLE). Subjects who decide to continue into the OLE will have the following additional procedures: 1) sign informed consent; 2) will be weighed; 3) will be instructed on study drug application; 4) will be given new diaries, and 5) will be provided with study drug.
c. A Follow-up telephone call will be made within 14 days after Day 90 to subjects who choose not to continue into the OLE.
d. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
e. IGA: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe.
f. VIIS scale for each body area: chest/abdomen, back, legs, and arms, for a possible overall score = 16.
g. Roughness (0-4 scale);
h. Palm/sole fissuring assessment: present/absent/number/pain (0-3 scale).
i. Photography will be performed at sites with the capability for subjects who sign a photographic ICF. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check.
j. ECG to be conducted at Screening, Baseline, Day 30, and Day 90 for all subjects. Subjects in the PK substudy will also have postdose ECGs at each serial blood draw on Day 1 and Day 30.
k. Subjects must be fasting (i.e., at least 8 hours)
l. Note: Subjects who are premenstrual at Screening but begin menses during the course of the study should follow the pregnancy testing schedule for WOCBP correlating to the visit menses began.
m. Samples for PK will be drawn from all subjects at Baseline and at each clinic visit. At selected sites among subjects who consent to participate in the PK substudy, samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1. On Day 30, IP will be applied in the clinic for PK substudy subjects, and PK samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose. Trough levels will be drawn when the subjects are in the clinic for other study visits (i.e., Day 14, Day 60, and Day 90). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.
n. Study staff will apply initial dose of study drug in the clinic after Baseline measurements, and the amount of study drug used will be measured (i.e., 36-g tube will be measured before and after application to determine amount used) to determine fixed dose.
o. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug tubes before dispensing; subjects must record days/times of study drug application in the diaries and any areas of skin not treated, e.g., due to local reactions). Dispense enough additional study drug until next visit (except at Day 90, unless subject consents to continue into OLE).
p. Confirm study drug compliance by measuring tube weight and reviewing diary.

Table 2-2: Schedule of Events for Open-label Extension

	Open-label Treatment Period						Follow-up
	Telephone Visit (Day 97)[a]	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7**	**8**		**9**	**10**	**11**
Week		**14**	**16**		**20**	**24**	**26**
Informed consent[a]							
Physical examination[b]						X	X
Vital signs (blood pressure and pulse)			X	X		X	X
Weight	X						
Record IGA[c]		X	X		X	X	X
VIIS[d] assessment		X	X		X	X	X
Roughness assessment[e]		X	X		X	X	X
Palm/sole assessment		X	X		X	X	X
Palm/sole fissuring assessment		X	X		X	X	X
Ectropion score			X	X		X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)[f]			X			X	
Pregnancy test for female subjects (urine)[g]			X		X	X	X
ECG			X			X	
PK blood sample collection[h]			X			X	
Application instructions, advice on emollient and sunscreen use[i]	X	X	X	X			

	Open-label Treatment Period						Follow-up
	Telephone Visit (Day 97)[a]	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7**	**8**		**9**	**10**	**11**
Week		**14**	**16**		**20**	**24**	**26**
Dispense study drug and diaries[j]		X	X		X		
Concomitant medications	X	X	X	X	X	X	X
Tolerability assessment		X	X		X	X	
Adverse events (and review diaries)	X	X	X	X	X	X	X
Collect all used/unused study drug[k]		X	X		X	X	

Abbreviations: ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears, nose, throat; ICF = informed consent form; IGA = Investigator's Global Assessment; PK = pharmacokinetic; OLE = open-label extension; VIIS = Visual Index for Ichthyosis Severity; WOCBP = women of childbearing potential

a. Subjects will sign the OLE ICF at the Double-blind Day 90/Week 12 Visit or within 7 days thereafter. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing and PK from Day 90/Week 12 will be carried over for the OLE and will not be repeated.
b. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
c. IGA: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe
d. VIIS scale for each body area: chest/abdomen, back, legs, and arms, for a possible overall score = 16.
e. Roughness (0-4 scale); fissuring assessment on palms/soles: present/absent/number/pain (0-3 scale).
f. Subjects must be fasting (at least 8 hours)
g. Subjects who are premenstrual at Screening but begin menses during the course of the study should follow the pregnancy testing schedule for WOCBP correlating to the visit menses began.
h. Samples for PK will be drawn from all subjects at Day 120 and Day 180. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.
i. Subjects must record days/times of study drug application in the diaries and any areas of skin not treated (e.g., due to local reactions).
j. All subjects in the OLE will receive trifarotene 200 µg/g. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug tubes before dispensing. Dispense enough additional study drug until the next visit (except at Day 180).
k. Confirm study drug compliance by measuring tube weight and reviewing diary.

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

3.2. List of In-Text Figures

REASONS FOR AMENDMENT

Protocol Amendment 1 is a major amendment that addresses feedback from the Regulatory Agencies, Competent Authorities, Central Ethics Committees, and investigators. The following changes were made:

1. Changed the primary endpoint to the Investigator's Global Assessment (IGA) and made the Visual Index for Ichthyosis Severity (VIIS) a secondary endpoint.
2. Aligned power calculation and parameter assumptions with the new primary endpoint.
3. Added optional photography evaluation of scoring by a central reader who is not a study investigator as a quality check.
4. Clarified body areas that should be excluded from treatment and/or assessment, and clarified dose adjustment for local tolerability and documentation thereof.
5. Clarified inclusion and exclusion criteria, and added that subjects with recent systemic malignancy (e.g., within 5 years) are excluded, with exceptions for those with nonmelanoma skin cancer or cervical intraepithelial neoplasia Grade 1 who are >6 months post-treatment.
6. Added exclusion criteria for subjects unable or unwilling to stop use of topical or systemic retinoids; institutionalized subjects, and subjects in any way related to the sponsor, investigator, or site personnel.
7. Specified that a legal guardian must sign an ICF for every minor.
8. Specified when the data safety monitoring board (DSMB) will meet and what data will be reviewed.
9. Added characterization of the investigational product.
10. Added background information about Study RD.03.SRE.40181E with CD5789 in subjects with ichthyosis.
11. Added rationale for 200 µg/g dose in OLE.
12. Added risk of absorption.
13. Added protective measures for risk of photosensitivity.
14. Specified that a tool will be supplied to apply investigational product to the back, and that if the investigational product (IP) is applied to the subject by someone other than the study subject, they should attend the first visit to learn how to apply it, and that hands must be washed immediately afterward or vinyl gloves should be used.
15. Specified windows and procedures for preventing blood draw contamination by the IP.
16. Specified that fissuring assessment is limited to palms/soles.
17. Added washout durations for keratolytics and monoclonal antibody medications, specified that washout includes physical treatments such as balneotherapy, and clarified that washout must be completed before study treatment begins.
18. Clarified that subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers.
19. Clarified that hormonal contraceptives must inhibit ovulation, and that abstinence relates to heterosexual intercourse and must be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
20. Revised the statistical analyses to reflect the change in endpoints.

21. Clarified permitted and prohibited therapies and medications, and use of standard of care treatment and timing thereof.
22. Specified that lamellar ichthyosis (LI) assessments must be done in order of presentation.
23. Revised descriptions of LI assessment tools scores (IGA and VIIS).
24. Defined fissures.
25. Clarified that investigators should use their judgment as to which quality-of-life tools should be used based on the subject's maturity.
26. Added a new section describing the photographic substudy.
27. Added electrocardiogram (ECG) for subjects in the PK substudy during serial blood draws on Days 1 and 30.
28. Clarified eligibility for OLE.
29. Reordered sections to put assessments in order of performance and renumbered all sections and lists accordingly.
30. Corrected duplicate endnote reference and typographical errors.

SUMMARY OF AMENDED SECTIONS

Section	Previous Text	Revision	Rationale
Synopsis and Section 7.1	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3-4 on a 5-point Visual Index for Ichthyosis Severity (VIIS) for scaling where 0 = clear and 4 = severe on at least 2 areas of the 4 body areas assessed (chest/abdomen, back, arms, and legs).	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point **Investigator Global Assessment [IGA)]** scale where 0 = clear; **1 = almost clear; 2 = mild; 3 = moderate;** and 4 = severe).	To follow FDA recommendation to use IGA as primary endpoint
Synopsis and Section 7.1	After the initial 15 subjects complete at least 28 days of treatment, an independent Data Safety Monitoring Board (DSMB) will review aggregate safety and tolerability data.	After the initial 15 subjects complete at least 28 days of treatment, an independent Data Safety Monitoring Board (DSMB) will review aggregate safety and tolerability data **(including PK and electrocardiogram [ECG] data).**	To clarify what data the DSMB will review
Synopsis and Section 7.1	All subjects who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE Period.	All subjects **(Cohort A and Cohort B)** who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE.	To specify that subjects from both double-blind cohorts will be eligible to continue into the Open-label Extension (OLE).
Synopsis, Section 7.1, and Section 10		Added: **Written informed consent will be obtained from a parent/legal guardian for any minor and minors will provide assent before any study-related procedures are performed.**	To ensure that parents/legal guardians sign ICF
Synopsis, Table 2-1, Sections 7.1, Section 9.8, and 10.2.1.2	After Screening, eligible subjects for Cohort A and B will enter a Washout Period of up to 35 days, during which they must stop using the following prohibited medications	**Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods, as applicable. Washout may be up to 3 months, as necessary**	To allow for full washout of any prohibited medications before randomization. Therapeutic baths can substantially improve scaling and affect the IGA evaluation.

Section	Previous Text	Revision	Rationale
		Added: **During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.** **After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.**	For psycho-social and functional reasons, and to not deter them from entering the study, allow subjects to use usual care on visible skin and on hands and feet. To exclude bathing to better assess moderate to severe LI and evaluate IGA on rest of body. To ensure subjects complete screening and eligibility within 35 days of randomization after any necessary washout.
Synopsis and Table 9-1		**Added a washout period of 2 weeks** for topical keratolytics (e.g., urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo. **Added a washout period for monoclonal antibody treatment (e.g., anti-IL17) of 5 half lives.**	To clarify length of the washout periods for these treatments.
Synopsis, Section 7.1, and Section 9.2	Thereafter, each subject will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of product in a tube. Subjects will record the date and time of study treatment administration in the subject diary.	Added: **If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.** **Subjects with heavy facial hair should not apply IP to hair-bearing areas.**	To specify areas not to be treated.

Section	Previous Text	Revision	Rationale
Synopsis		Added: **If the treatment causes application site reactions, the frequency of application will be reduced or interrupted only on the area concerned, as indicated herein.**	To clarify dose adjustment and evaluation.
Synopsis, Table 2-1 footnote, and Section 9.4	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for stinging/burning, pruritus, erythema) and the following procedures will be followed:	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for stinging/burning, pruritus, erythema) **for each body area (chest/abdomen, back, arms, legs, and face/neck)** and the following procedures will be followed:	To clarify areas to be assessed for local tolerability.
Synopsis and Section 9.4	– If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on this area only once weekly, until the score is back to <2. – If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3.	– If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area **(e.g., the face)**, the study drug will be applied on this area only once weekly, until the score returns to <2. **Continue to treat all other areas twice weekly provided the score is <2 on those areas.** – If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 **(i.e., "drug holiday"). Continue to treat all other areas twice weekly provided the score is <2 on those areas.** **Any changes in dosing must be documented in the subject diary and the eCRF.**	To clarify dose adjustment for local tolerability, and how it should be documented.

Section	Previous Text	Revision	Rationale
Synopsis and Section 10.1		Added: **Written informed consent will be obtained from a parent/legal guardian for any minor and minors will provide assent before any study-related procedures are performed.**	To clarify that a legal guardian must sign an ICF for every minor.
Synopsis and Section 7.1, and Section 10.3.1.9	Photographs will be taken at Baseline, Day 30 and Day 90 at selected sites with photographic capability for subjects who sign a separate photographic informed consent form (ICF).	**At all sites with photographic capability** photographs will be taken **as source data to support scoring** at Baseline, Day 30, and Day 90. **A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will** sign a separate, **optional** photographic informed consent form (ICF).	To obtain photographic evidence, where possible, for confirmation of scoring consistency, as assessed by a central reader.
Synopsis and Section 7.1		Added: **Visits for PK must occur at least 24 hours after the last application of the study drug, to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.**	To ensure pharmacokinetic (PK) blood draws are not contaminated with IP.
Synopsis and Section 7.1	In addition, a PK substudy will be conducted at specific sites with the capability to conduct it.	In addition, a PK substudy will be conducted **on Days 1 and 30 at sites with the capability to conduct it.** Added: **For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30.**	To clarify on which days the PK substudy will be performed, and that postdose ECGs will be performed during serial sampling on those days (per MHRA request).
Synopsis and Section 8.2.1	Inclusion criterion #3: Subject has moderate to severe (VIIS 3-4) LI on at least 2 of the 4 body areas assessed (chest/abdomen, back, arms, and legs).	Inclusion criterion #3: Subject has moderate to severe (**IGA 3-4**) LI on **the IGA** of LI severity.	To follow FDA recommendation to change primary endpoint to IGA.

Section	Previous Text	Revision	Rationale
Synopsis and Section 8.2.1	Inclusion criterion #7: • combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline OR Agrees to abstain from sex during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study.	Inclusion criterion #7: • combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline**; hormonal contraceptives must inhibit ovulation** • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline OR Agrees to abstain from **heterosexual intercourse** during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. **Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.**	To align with Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials, per MHRA.
Synopsis and Section 8.2.2	Exclusion criterion #2: Subject has a history of or current moderate or severe stinging/burning at Screening.	Exclusion criterion #2: Subject has ~~**a history of or**~~ current moderate or severe stinging/burning at Screening.	To clarify that history of stinging/burning does not prevent enrollment.
Synopsis and Section 8.2.2	Exclusion criterion #4: Subject with a known lipid disorder unless well controlled by stable doses of lipid-lowering agents for at least 6 months.	Exclusion criterion #4: Subject with a known lipid disorder **(hypertriglyceridemia >200 mg/dL, hypercholesterolemia >250 mg/dL)** unless well controlled by stable doses of lipid-lowering agents for at least 6 months.	To group all lipidema criteria together.

Section	Previous Text	Revision	Rationale
Synopsis and Section 8.2.2	Exclusion criterion #5: Subject was previously treated with trifarotene/CD5789, including the acne formulation, or participated in previous studies for ichthyosis.	Exclusion criterion #5: Subject was previously treated with trifarotene/CD5789 **in an acne or ichthyosis study.**	To avoid restricting enrollment.
Synopsis and Section 8.2.2	Exclusion criterion #6: Subject has known skeletal disease, hypertriglyceridemia, hypercholesterolemia, liver disease, or other poorly controlled medical conditions.	Exclusion criterion #6: Subject has **any other significant concomitant disease**, or poorly controlled medical **condition other than LI that, in the investigator's opinion, may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments**.	To add hypertriglyceridemia and hypercholesterolemia as exclusion criteria and combine Exclusion Criterion #4 and Exclusion Criterion #7 to avoid restricting enrollment
Synopsis and Section 8.2.2	Exclusion criterion #7: Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome), Crohn's disease, or any other significant concomitant disease other than LI that, in the investigator's opinion, may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments	Exclusion criterion #7: Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, **Cushing syndrome, Crohn's disease, or ulcerative colitis).**~~any other significant concomitant disease other than LI that, in the investigator's opinion, may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments~~	To exclude subjects with conditions that may affect skeletal integrity.
Synopsis and Section 8.2.2	Exclusion criterion #8: Subject is being treated for major depression disorder	Exclusion criterion #8: Subject is being treated for major depression disorder **and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts.**	To define major depressive disorder and to allow subjects with treated mild depression to be enrolled.

Section	Previous Text	Revision	Rationale
Synopsis and Section 8.2.2	Exclusion criterion #10: Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory b. Triglycerides >200 mg/dL c. Total cholesterol >250 mg/dL d. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women e. Platelets <150 × 10^9/L or >400 × 10^9/L	Exclusion criterion #10: Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory **b. Total bilirubin >1.1 mg/dL or, in case of Gilbert's syndrome, total bilirubin >3 mg/dL** c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women d. Platelets <150 × 10^9/L or >400 × 10^9/L	Moved triglycerides and total cholesterol to Exclusion Criterion #4 and add total bilirubin and Gilbert's syndrome (per MHRA request).
Synopsis and Section 8.2.2		Added**:** Exclusion criterion #12: **Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment.**	To exclude subjects with recent systemic malignancies.
Synopsis and Section 8.2.2		Added**:** Exclusion criterion #17: **Subject is unable or unwilling to stop use of topical or systemic retinoids**.	To exclude subjects using topical or systemic retinoids, per MHRA request.
Synopsis and Section 8.2.2		Added: Exclusion criterion #20: **Subject is institutionalized** Added: Exclusion criterion #21: **Subject is in any way related to the sponsor, investigator, or site personnel.**	To exclude vulnerable or biased subjects

Section	Previous Text	Revision	Rationale
Synopsis, Section 7.1, and Section 10.3	Primary efficacy endpoint: The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0-4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs).	Primary efficacy endpoint: The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear **on treated areas and at least a 2-grade change** from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period **on the 5-point IGA full body scale.**	To follow FDA recommendation to change primary endpoint from VIIS to IGA.
Synopsis and Section 13.1.4.1	The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear on treated areas and at least a 2-grade change from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA full body scale. The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0 4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs). Secondary endpoints: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices:	The **proportion** of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear on treated areas and at least a 2-grade change from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA full body scale. Secondary endpoints: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices **from baseline through Week 12**: – **5-point Visual Index for Ichthyosis Severity (VIIS) scale for scaling from Baseline through Week 12 (overall 16 points for scaling, i.e. 0-4 points for 4 body areas: chest/abdomen, back, arms and legs)** – Individual score for roughness (Scale: 0–4) overall – Palm/sole Assessment (Scale: 0–4)	To reflect change in endpoints; IGA is now primary endpoint (and thus, no individual scaling score is needed), and VIIS is a secondary endpoint. To limit fissure evaluation to the palms/soles. To clarify endpoints for statistical analysis. To add the children's versions of the DLQI (cDLQI) and EQ-5D (EQ-5D-Y)

Section	Previous Text	Revision	Rationale
	– Palm/sole Assessment (Scale: 0–4) – Individual score of scaling (Scale: 0–4) – Individual score for roughness (Scale: 0–4) overall • The difference in proportion of subjects with presence of fissures (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) between the active trifarotene cream HE1 and vehicle groups. • Quality of life per EQ-5D-5L • The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups • Quality of life per DLQI	– Quality of life per DLQI and cDLQI • The difference in proportion of subjects with presence of fissures **on palms/soles** (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) **at Week 12** between the active trifarotene cream HE1 and vehicle groups. • The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups **from Baseline through Week 12** • The **difference in quality** of life per EQ-5D-**5L and EQ-5D-Y** scores **between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12**	
Synopsis	Safety endpoints: • Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs • Local tolerability (Scale: 0-3 [none, mild, moderate, severe], determined by the investigator)	Safety endpoints: • Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs • Local tolerability (Scale: 0-3 [none, mild, moderate, severe], determined by the investigator) **for each body area (chest/abdomen, back, legs, arms, and face/neck).**	To clarify that tolerability will be assessed on all body areas where the treatment is applied.
Synopsis and Section 13.1.4.2	The intent-to-treat (ITT) population will comprise all randomized subjects. The modified intent-to-treat (mITT) population comprises all subjects in the safety	The intent-to-treat (ITT) population will comprise all randomized subjects. **This population will be used as the primary population for the analysis of efficacy for the**	To clarify that the intent-to-treat population will be used for the primary analyses of efficacy for the double-blind period.

Section	Previous Text	Revision	Rationale
	population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT in the Double-blind Period will be presented. Generalized estimating equations (GEE) for binary response will be used to model the odds of successful resolution of LI with treatment group as a predictor. Other covariates, such as baseline IGAVIIS scores, baseline characteristics, and interactions may be included. Various correlation matrix structures will be explored to model the within subject correlation. Additionally, the difference in mean VIIS score at Week 12/EOT between the active trifarotene cream HE1 groups and vehicle group will be analyzed using a 2-sided, 2-sample Wilcoxon rank-sum test at the 5% significance level; 95% confidence intervals will be presented. The VIIS scores as well as secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Week 24.	**Double-blind Period of the study.** The modified intent-to-treat (mITT) population comprises all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. The number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT in the Double-blind Period will be presented. **The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group, 95% CIs for the differences, and P-values for the differences in treatment will also be presented.** The **IGA** scores as well as **continuous** secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Week 24. Deleted: Frequencies of results and 95% confidence intervals will also be reported, and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test.	To follow change in primary endpoint and addition of secondary endpoints.

Section	Previous Text	Revision	Rationale
Synopsis and Section 10.1.1	Screening and washout: Up to 35 days	Screening: Up to 35 days **(after signing informed consent, if necessary, washout may be up to 3 months, and subjects should return to the site after washout to complete the study eligibility requirements)**	To allow for full washout of any prohibited medications before randomization.
Synopsis and Section 13.2	Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) using a 2-sample t-test assuming a mean difference of at least 1.0 and a standard deviation of 1.4 or lower.	Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) **using a 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively.**	To align power calculation and parameter assumptions with the new primary endpoint.
Table 2-1	Screening (-35 days to -1 day)	Screening (-35 days to -1 day) **Washout up to 3 months** **Added footnote a: Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods, as applicable. Washout may be up to 3 months, as necessary. During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower but not bathe or swim during the Screening Period. After completing any necessary**	To allow for full washout of any prohibited medications before randomization.

Section	Previous Text	Revision	Rationale
		washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.	
Table 2-1	Schedule of Events for Double-blind Period	Reordered assessments of IGA, VIIS, and roughness to be in order of conduct. Added **"palm/sole"** to fissuring assessment. Changed "assign randomization number" to "**Randomization via IWRS**." Added "**and sunscreen**" to advice on emollient use. Changed complete physical examination to be done at Screening and limited physical examinations at other time points as indicated. Changed height, weight, and BMI to be done at Screening instead of Baseline. Added abbreviation IWRS and definition. Added to footnote: Photography will be performed at sites with the capability for subjects who sign a photographic ICF. **A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check.** Added to footnote **subjects in PK substudy will have postdose ECG at each serial blood draw on Day 1 and Day 30**. Added to footnote: **Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the**	To clarify that IGA should be performed first and all efficacy assessments should be performed in the order in which they are listed within the protocol. To limit fissure evaluation to the palms/soles. To specify that randomization will be conducted via IWRS to avoid confusing site personnel. To include sunscreen to instructions regarding emollient use. To clarify when physical examinations and height, weight, and BMI are performed. To specify that a central reader will assess the photographs as a quality check of scoring consistency from Days 30 and 90. To ensure postdose ECGs are collected (per MHRA advice) for subjects in PK substudy during serial sampling. To ensure PK samples are not contaminated by recent application of study drug.

Section	Previous Text	Revision	Rationale
		skin after the last application.	
Table 2-2	Schedule of Events for Open-label Extension	**Revised footnote to IGA criteria**. Reordered and revised assessments	To specify order of assessment performance and that assessment of scaling is no longer done, and to clarify that fissuring only applies to palms/soles.
Section 5.2		Added: **One study was conducted with CD5789 50 µg/g, 100 µg/g, and placebo in subjects with icthyosis (Study RD.03.SRE.40181E). Among 31 subjects treated in this study, 17 were treated with CD5789 100 µg/g, and 14 were treated with 50 µg/g (all subjects received placebo [vehicle] on the contralateral zone). Mean (SD) baseline IGA score was 5.7 ± 1.6 among the 31 subjects. Improvement in the investigator's global assessment (IGA) of scaling and roughness was observed by Day 8 with both doses. The primary efficacy criterion was the change in IGA from the Baseline Visit (Day 1) to the Final Visit (Day 43). At Endpoint (intent-to-treat population, last observation carried forward [LOCF]), the CD5789 100 µg/g group had a statistically significant decrease from Baseline in IGA compared with Vehicle (-1.4±2.2; p=0.018) (Investigator's Brochure for CD5789 Cutaneous Formulation).** Added: **However, it is possible that absorption in subjects with LI may be greater than in healthy**	To add experience with CD5789 in subjects with ichthyosis and to clarify that systemic absorption may differ in subjects with ichthyosis.

Section	Previous Text	Revision	Rationale
		volunteers, due to the skin being compromised. **Based on these data, both the 100 µg/g and 200 µg/g doses showed an acceptable safety profile and will be used in this phase 2 LI study, to determine which of the 2 doses is most effective. The open-label extension (OLE) will evaluate the long-term safety of the higher dose in this patient population.**	
Section 5.3	The potential risks of study participation include those associated with exposure to tifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture.	The potential risks of study participation **for all subjects** include those associated with exposure to trifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture. **The study population will comprise adults and adolescents aged 12 to 17 years.** Added: **In addition, subjects should take protective measures such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet), and/or seeking shade or shelter from the sun.** Added: **No clinically significant systemic risks associated with CD5789 have been identified. Given the mechanism of action for CD5789 Cream HE1, it is assumed that efficacy will increase as the dose is increased. As such, the 200 µg/g dose was selected for the OLE based on its previously established safety profile, expected superiority to placebo and 100 µg/g. However the Data Safety Monitoring Board (DSMB),**	To specify protective measures for avoiding sunlight/UV light (per MHRA request). To include systemic risks, and to add that the DSMB applies to both parts of the study and that if the 200 µg/g dose causes safety issues, the protocol will be amended if necessary.

Section	Previous Text	Revision	Rationale
		who will routinely review aggregate safety and tolerability data, as well as any safety concerns brought to the their attention by the study investigators or medical monitor, may determine that the study should be modified, placed on hold, or stopped if serious safety issues are discovered. This is applicable for both the double-blind portion and OLE. If the 200 µg/g dose in raises any safety concerns, the protocol will be amended and the dose will be reduced.	
Section 7.1	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe**])** averaged over the BSA and will follow the procedures detailed in Section 9.4	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) **for each treated body area (chest/abdomen, back, legs, arms, and face/neck)** and will follow the procedures detailed in Section 9.4	To clarify that local tolerability assessments will be performed on all treated areas.
Figure 7-1		Redrawn	Removed extraneous arrows; improved layout
Section 8.4	An investigator may discontinue a participant's study treatment for any of the following reasons • If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant	An investigator **must** discontinue a participant's study treatment for any of the following reasons • If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would **result in a significant burden to** the participant	To clarify that this is mandatory. To clarify that these would be burdensome to the participant.
Section 9.1		Added: **It is a potent RARγ agonist characterized by its high specificity to this receptor.**	To further characterize the investigational product.

Section	Previous Text	Revision	Rationale
Section 9.2		Added: **The IP should be applied thinly and gently rubbed in.** Added: **If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.**	To clarify how IP should be administered. To clarify that anyone other than the study subject, who may apply the IP to the subject, is trained on application of IP.
	Subjects should not apply IP on visit days until after the visit.	Added: **Persons other than the study subject applying the study drug must wash their hands after application or use disposable vinyl gloves. In addition, a long-handled applicator will be provided for application on the back. The applicator must be washed with warm water and soap after every application.** **Trifarotene cream should not come into contact with the eyes, mouth, angles of the nose, or mucous membranes. For the ectropion treatment, Q-tips are recommended for precise application on eyelids, without contact to the eye or conjunctiva. If the IP gets into the eye, it must be flushed immediately with warm water. In case of eye irritation, the subject must be seen by an ophthalmologist.**	To specify areas not to be treated. To ensure the safety of others who may apply the IP to the study subject and to improve application. To ensure PK blood draws are not contaminated with IP.

Section	Previous Text	Revision	Rationale
		At least 24 hours must have elapsed since last IP administration before PK blood draws are performed. Subjects should not apply IP to the area where blood will be drawn for at least 24 hours before the next PK sample draw. Subjects should not apply IP on visit days until after the visit, **unless they are participating in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the blood draw. Among subjects participating in the PK substudy, ensure the PK line is inserted before study drug application to prevent contamination with the IP and protect the skin around the needle insertion point from study drug application.**	
Section 9.3		Added: **Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application. Subjects should not apply the IP on visit days until after the visit, unless they participate in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the PK blood draw.**	To ensure PK blood draws are not contaminated with IP.
Section 9.4.1		Added: **Any changes in dosing must be documented in the subject diary and the eCRF.**	To ensure documentation of any dosing changes.

Section	Previous Text	Revision	Rationale
Section 9.5		Added: **Subjects who taper to once weekly application or who take a "drug holiday" for tolerability will not be reported as having deviated from the protocol (see Section 9.4 for dose adjustment and stopping rules); any changes in dosing must be documented in the subject diary and the eCRF.**	To clarify that subjects who require dose adjustment because of local tolerability will not be counted as having deviated from the protocol.
Section 9.7	Unblinding should be discussed in advance with the medical monitor, if possible.	**The investigator may discuss with the medical monitor in advance of unblinding a subject,** if possible, **if it is not deemed as an emergency**. **However, the investigator has the ultimate decision for unblinding a subject for medical treatment and no procedures will prevent or delay necessary unblinding in an emergency for the subject's safety**.	To clarify that the investigator has the authority to make decisions about unblinding a subject (per MHRA recommendation).
Section 9.8.1	Subjects will be advised on permitted emollient(s) for use on nontreatment days during the study; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited.	Subjects will be advised on permitted emollient(s) for use **as often as needed** on nontreatment days during the study**; on treatment days, the use of emollient(s) is permitted except within 4 hours before or after study drug application. Similarly, protective sunscreen should be applied as often as needed, except within 4 hours before or after study drug application. Subjects may use their standard of care treatment on their faces and/or palms/soles after the Week 4 assessment if they experience a worsening of IGA in those areas. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. These standard of care treatments should be approved by the investigator and documented in the eCRF.**	To clarify when use of emollients and protective sunscreen is permitted. To add sunscreen as protection from sunlight/UV light. To allow subjects who experience worsening of IGA to return to standard of care treatment, as approved by the investigator, after Day 30. To avoid combination treatment during the OLE (no washout is necessary). Standard of care is permitted after the OLE Week 16 visit, as long as it does not contain prohibited medications,

Section	Previous Text	Revision	Rationale
		Subjects who enter the OLE must stop standard of care treatment. If they experience a worsening of IGA they may use standard of care treatment on their faces and/or palms/soles after the Week 16 visit if the standard of care does not contain prohibited medications. If those standard of care treatments include prohibited medications, the subject should be discontinued from the study.	
Section 9.8.2	The therapies listed in Table 9-1 are prohibited during the study.	The **medications** listed in Table 9 1 are prohibited during the study. Added: **Balneotherapy is also prohibited during the Screening Period and during the study.** Added: **Use of benzoyl peroxide is permitted on non-treatment days for subjects with concomitant acne only; it must not be applied on treatment days due to risk of inactivation of trifarotene by benzoyl peroxide.** Added: **For enrolled subjects who require prescription of a systemic azole, the principal investigator should discuss with the medical monitor whether the subject may continue in the study.**	To allow subjects with acne to use benzoyl peroxide on nontreatment days. To specify that physical treatments such as balneotherapy are also prohibited. To specify that if subjects are prescribed an azole after study enrollment, their continued participation must be discussed with the medical monitor.

Section	Previous Text	Revision	Rationale
Section 9.8.3	Subjects should not shower, bathe, or swim within 4 hours of after study drug application. No occlusive dressings should be applied to areas where study drug was applied. Subjects should only use investigator-approved emollients, and should not use them on treatment days within 4 hours of study drug application.	Subjects should not shower, bathe, or swim **for at least** 4 hours after study drug application. No occlusive dressings should be applied to areas where study drug was applied. Subjects should only use investigator-approved emollients, and should not use them on treatment days **for at least** 4 hours **before and after study drug** application. Added: **In addition, subjects should take protective measures to avoid exposure of treated areas to sunlight, such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet), and/or seeking shade or shelter from the sun.**	To clarify the window for showering or bathing and use of emollients on treatment days. To improve safety with regard to exposure to sunlight/UV light.
Section 10.2		Added: **It is suggested that quality of life assessments be conducted first to avoid any bias, and that the IGA be recorded as the first LI assessment at every visit.**	To clarify order of assessment and to ensure IGA is recorded first as primary efficacy endpoint.
Section 10.2.1.1	Subjects must be screened within 35 days before randomization in the study. The following procedures will be performed at Screening	The subject must **complete eligibility screening** within 35 days before randomization in the study. The following procedures will be performed **during** Screening Reordered assessments to be in order of performance**.** Revised assessments to exclude individual scaling, to limit fissuring to palms/soles, and to add photographs as source documents**.**	To reflect that subjects who require washout may return to the site to complete eligibility assessments within 35 days of randomization. To reflect the changes in primary and secondary endpoints, the limit of fissuring to palms/soles, and the addition of photographs as source documents, and to ensure the order of assessments is correct.
Section 10.2.2.1		Reordered assessments to be in order of performance.	To specify order of assessments; to specify that randomization is via

Section	Previous Text	Revision	Rationale
		Revised assessments to exclude individual scaling, to limit fissuring to palms/soles, and to add cross-reference to Sections 10.3.1.5 and 10.3.1.6. Specified randomization to be done via IWRS. Added caution to **ensure that PK lines are placed before IP application**. Added instructions **if the product will be applied at home by someone other than the study subject.** Added **sunscreen(s**) use on nontreatment days and time frame for use on treatment days. Added: **Among subjects in the PK study, perform an additional ECGs at times of serial sampling.**	the IWRS,; to specify that fissuring is only to be assessed on palms/soles, to provide location of specific quality of life scales, to specify procedures and times for PK serial blood draws to prevent contamination with IP, to ensure persons other than the study subject who may apply IP to the study subject are trained in IP application procedure; and to specify when emollients and protective sunscreen may be used on treatment days.
Section 10.2.2.2 and Section 10.2.2.5	Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit.	Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) **and/or sunscreen(s)** on study drug treatment days within 4 hours **before or after** study drug application is prohibited), and remind subjects **that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should** not apply IP on visit days until after the visit.	To specify when emollients and protective sunscreen may be used on treatment days, and to add a window for IP application before next visit to prevent IP-contamination of PK blood samples.
Sections 10.2.2.3, 10.2.2.4, 10.2.2.6, and 10.2.2.7		Reordered assessments to be in order of performance. Revised assessments to exclude individual scaling, to **limit fissuring to palms/soles**, and to add cross-reference to Sections 10.3.1.5 and 10.3.1.6. Added **sunscreen(s)** use on nontreatment days and time frame for use on treatment days.	To specify order of assessments; to specify that fissuring is only to be assessed on palms/soles; to provide location of specific quality of life scales; to specify when emollients and protective sunscreen may be used on treatment days, and to add a window for IP

Section	Previous Text	Revision	Rationale
		Added reminder that **24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.**	application before next visit to prevent IP-contamination of PK blood samples.
10.2.2.4		Added caution to **ensure that PK lines are placed before IP application.** Added: **Among subjects in the PK study, perform an additional ECGs at times of serial sampling.**	To specify order of assessments; to specify that fissuring is only to be assessed on palms/soles; to provide location of specific quality of life scales; to specify procedures and times for PK serial blood draws to prevent contamination with IP; to add postdose ECGs for subjects in PK substudy; and to specify when emollients and protective sunscreen may be used on treatment days.
Section 10.2.2.7	For subjects who successfully complete the initial 12 weeks of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study.	For subjects who successfully complete **(i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion)** the initial 12 weeks of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study.	To define "successful completion" of the Double-blind Period and to clarify eligibility for OLE.
Section 10.2.4	Subjects who complete the 12-week Double-blind Treatment Period of the study may choose to continue into an optional 12-week Open-label Extension with trifarotene cream HE1 200 µg/g.	Subjects who **successfully** complete **(i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion)** the **initial 12 weeks of double-blind treatment** may choose to continue into an optional 12-week OLE with trifarotene cream HE1 200 µg/g.	To clarify eligibility for OLE.

Section	Previous Text	Revision	Rationale
Section 10.2.4.2 – 10.4.2.7		Reordered assessments to be in order of performance, and revised assessments to **limit fissuring to palms/soles**. Added **sunscreen(s)** use on nontreatment days and time frame for use on treatment days. Added reminder that at least **24 hours must have elapsed since IP application before the subject's next PK blood draw**.	To specify order of assessments; to specify that fissuring is only to be assessed on palms/soles. To specify when emollients and protective sunscreen may be used on treatment days. To add a window for IP application before next visit to prevent IP-contamination of PK blood samples.
Section 10.3	The 5-point VIIS is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. The VIIS scale was developed to generate a reliable method to assess ichthyosis clinical severity using solely scale and erythema, which are the only findings present in ichthyosis of every genetic cause, and occur either upon skin of normal thickness (lamellar subtypes) or upon thickened skin (keratoderma subtypes).[13] The VIIS uses a 5 point index to assess the level of severity of scale and erythema in each of 4 body areas: chest/abdomen, back, legs, and arms, for a possible overall total of 16 points (Section 10.3.1.1).	The 5-point **IGA** is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. **The IGA scale was developed with the support of experts from academic reference centers for the treatment of ichthyosis. Each level of severity will consider both the severity of scaling and the severity of roughness** (Section 10.3.1.1).	To reflect the change in primary endpoint to IGA.
Section 10.3.1.1	10.3.1.1 Visual Index for Ichthyosis Severity – Scaling The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/EOT on	10.3.1.1 **Investigator's Global Assessment** The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear **and at least a 2-grade change from Baseline at Week 12/EOT in the Double-blind Period on**	To reflect the change in primary endpoint to IGA and that fissuring will only be assessed on palms/soles.

Section	Previous Text	Revision	Rationale
	the overall 16-point VIIS for scaling. The investigator will rate the subject's condition using the 5-point VIIS for each body area (chest/abdomen, back, legs, and arms) and an overall score at each time point shown in the Schedule of Events (Section 2.2): 0 Clear Normal skin; no perceptible scale or smoothening 1 Almost clear Areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum) 2 Mild Confluent smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum) 3 Moderate Confluent scales (visibly separated/fractured stratum corneum) including some large (>1cm), thick scales 4 Severe Confluent, primarily large, thick scales	**the 5-point IGA full body scale.** The investigator will rate the subject's condition using the 5-point **IGA** at each time point shown in the Schedule of Events (Section 2.2). **The IGA will be measured on a 5-point scale, excluding the following areas: knees, elbows, neck, palms, soles, axillae, groin, and scalp**: 0 Clear **No scaling and no roughness** 1 Almost Clear **Occasional fine scales; hardly palpable roughness (mostly smooth**) 2 Mild **Small and fine scales predominate; no more than a few large scales; mild roughness on palpation** 3 Moderate **Some large scales that may be thick; coarse roughness on palpation** 4 Severe **Confluent, primarily large (>1 cm), thick scales with plate-like hyperkeratosis**	

Section	Previous Text	Revision	Rationale
Section 10.3.1.2	10.3.1.2 Investigator's Global Assessment	Changed to : 10.3.1.2 **Visual Index for Ichthyosis Severity – Scaling** The ~~primary~~ **secondary** endpoint is the number of subjects in each treatment group who experience a severity score of 0 or 1 ~~and at least a 50% reduction from Baseline~~ at Week 12/EOT on **the overall 16 point VIIS for scaling**. The investigator will rate the subject's condition using the **5-point VIIS for each body area (chest/abdomen, back, legs, and arms)** and an overall score at each time point shown in the Schedule of Events (Section 2.2). Deleted **clear/almost clear/mild/moderate/severe** from scoring scale.	To reflect the change in primary endpoint to IGA.
Section 10.3.1.3	Individual Score of Scaling (Scale: 0-4)	Changed to: Individual Score **for Roughness**	No individual score for scaling is needed now that IGA is primary endpoint.
Section 10.3.1.5		Added: **A fissure is a longitudinal and deep crack that separates the stratum corneum and may penetrate down to the dermis, causing pain and sometimes bleeding.**	To clarify the definition of a fissure.

Section	Previous Text	Revision	Rationale
Section 10.3.1.6	The DLQI is a dermatology-specific Quality of Life instrument.	10.3.1.6 Dermatology Life Quality Index The DLQI is a dermatology-specific Quality of Life instrument **for subjects aged 17 years and older (1992). The child DLQI (cDLQI; May 1993) is for subjects aged 12 to 16 years.** Added: **The investigator should use his or her judgment of the maturity of the subject to decide which version of the questionnaire to use; the same version must be used for the subject throughout the study.**	To specify which DLQI instrument should be used based on the investigator's judgment of the study subject's maturity.
Section 10.3.1.7	The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS). The EQ VAS records the subject's self-rated health on a vertical VAS.	The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS). **The EQ-5D-5L (2009) is intended for use in adult subjects, while the EQ-5D-Y (2012) is to be used for children and adolescents.** Added: **The investigator should use his or her judgment of the maturity of the subject to decide which version of the questionnaire to use; the same version must be used for the subject throughout the study.**	To specify which EQ-5D instrument should be used based on study subject age, and to clarify the VAS is 0-100.
Section 10.3.1.8		Added: **Figure 10-1 Ectropion Severity Score** (from reference #14)	To show how the ectropion score should be calculated.

Section 10.3.3	Sample Collection: Blood: Each blood sample will be 3 mL/kg in volume. The total amount of blood to be drawn for serial PK assessments will be a maximum of 5 mL/kg per subject over a 24-hour period.	Added: **Finding veins in subjects with this disease can be challenging. Blood draws will be done at the corresponding study visits before application of the IP and should be 24 hours after IP application. Subjects must not apply the IP to the area where blood will be drawn within 24 hours before their next study visit to avoid contamination of the blood by IP that remained in the skin. For subjects in the PK substudy, a cannula should be placed before IP application and the cannula site may be occluded to prevent contamination with IP.** **Actual PK sample times for subjects in the PK substudy will be recorded in the eCRF.** Blood: **For subjects not in PK substudy:** **The expected amount of blood to be drawn at each visit varies from approximately 6 mL to a maximum of 21 mL (Screening Visit only). The total amount of blood drawn for the study will be about 123 mL per subject, unless the subject takes part in the PK substudy.** **For subjects in PK substudy:** **For subjects who opt to participate in the PK substudy, extra blood samples will be drawn at Visit 2 and at Visit 4 for PK analysis. The amount of blood to be drawn per subject at each of these visits will be approximately 54 mL. For subjects taking part in the substudy, the total amount of blood drawn for**	To clarify how blood draws should be performed to prevent contamination with IP.

Section	Previous Text	Revision	Rationale
		the entire study will be approximately 195 mL.	
Section 10.3.4.2.2		Added: **Gel ECG electrodes may be used for ECGs because they are more conductive and cause less trauma on compromised skin. Efficacy assessments should be conducted before ECGs to avoid possible artefact/changes from the ECG.** **For subjects in the PK substudy, additional ECGs will be performed postdose during serial blood sampling on Day 1 and Day 30.** **If there is a marked prolongation of the QT/QTc interval during treatment, a subject should be discontinued from the IP, but remain in the study until full resolution of the event. The DSMB will be informed immediately of such an occurrence.**	To ensure the most comfortable method is used; to address order of assessments; to add ECGs postdose at Day 1 and Day 30 (per MHRA request) among subjects in the PK substudy; and to address procedures should QT/QTc prolongation occur.
10.3.4.2.3	A complete physical examination excluding the genitourinary examination will be performed as indicated in the Schedule of Events (Section 2.2).	A complete physical examination excluding the genitourinary examination **will be performed at Screening, while limited physical examinations (to include HEENT, cardiorespiratory, abdomen, and range of motion)** will be performed as indicated in the Schedule of Events (Section 2.2).	To clarify when complete and limited physical examinations are to be performed.
Section 10.3.4.2.4	All application site reactions will be recorded as AEs.	All application site reactions will be recorded as **TE**AEs **in the diary. These should include the date and severity of the TEAE.**	To specify that all application site reactions should be recorded in the subjects' diaries in detail.
Section 11.2.3		Added: **Any AE that occurs during the Screening Period will be captured as such on the AE page of the eCRF (not medical history).**	To clarify that any AE that occurs after signing of the ICF is to be captured as such and not as medical history.

Section	Previous Text	Revision	Rationale
Section 11.3.2	All WOCBP who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation.	All WOCBP who participate in the study should be counseled on the need to practice **highly effective** birth control and on the importance of avoiding pregnancy during study participation. Added: **Among the clinical studies, 12 pregnancies were reported: 4 resulted in normal births; 5 resulted in spontaneous abortions (none of which was considered related to CD5789); 1 was electively aborted, and 2 were lost to follow-up (Investigator's Brochure for CD5789 Cutaneous Formulation).**	To clarify that birth control must be "highly effective" (per MHRA). To add data on pregnancy from clinical studies with CD5789.
Section 12	The DSMB will meet after subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data. The data will remain blinded unless an issue or trend arises that requires unblinding. At that time, the DSMB will decide whether Cohort B (adults and subjects aged 12–17) may begin enrolling. The DSMB will have the authority to recommend to the sponsor that the study be placed on hold, or discontinued if serious safety issues are discovered.	The DSMB will meet after **15** subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data **(including PK and ECG results)**. The **safety** data will **be un**blinded. At that time, the DSMB will decide whether Cohort B (adults and subjects aged 12–17) may begin enrolling, or if additional adult safety data are required before allowing subjects aged 12 – 17 to participate in the study. The DSMB will have the authority to recommend to the sponsor that the study be **modified**, placed on hold, or **stopped** if serious safety issues are discovered. Added: **Any protocol changes the DSMB may suggest will be submitted to all applicable regulatory bodies for review and approval.**	To clarify when the DSMB will meet, and what data they will review.
Section 13.1.2.2 and Section 13.1.3		Added: **Subjects who taper to once-weekly application or who take a "drug holiday" will not be reported as having deviated from the protocol.**	Clarified that subjects requiring dose adjustment or temporary interruption are not protocol deviators.

Section	Previous Text	Revision	Rationale
Section 13.1.2.3	Baseline subject characteristics will include medical history, physical examination findings, and **VIIS** score.	Baseline subject characteristics will include medical history, physical examination findings, and **IGA** score.	To reflect change in primary endpoint to IGA.
Section 13.1.4	The mITT population will be used as the primary population for the primary analysis of efficacy at Week 12. All efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE using the OLE mITT and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE.	The **ITT** population will be used as the primary population for the primary analysis of efficacy at Week 12. **Select** efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE using the **OLE ITT,** OLE mITT, and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE	
Section 13.1.4.2	Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from baseline will be provided for VIIS scores for both periods.	Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from baseline will be provided for **IGA** scores for both periods.	To reflect the change in primary endpoint to IGA.
Section 13.1.4.3	Additionally, for the Double-blind Period only, change from Baseline endpoints through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate. Frequencies of results and 95% CIs will also be reported and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test.	Additionally, for the Double-blind Period only, change from Baseline **in continuous secondary endpoints** through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate. Added: **The proportion of subjects with at least a 50% reduction in IGA score from Baseline will be analyzed using the same logistic regression analysis described in Section 13.1.4.2.**	To reflect and clarify changes in secondary endpoints.

Section	Previous Text	Revision	Rationale
Section 13.1.4.5	To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using LOCF for the Double-blind Period only. Imputation will not be performed in the OLD period.	To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using **multiple imputation (MI)** for the Double-blind Period only. **Multiple-imputations will be used to replace missing IGA outcomes using multiple draws from the posterior predictive distribution estimated from the treatment groups. IGA scores will be imputed and then categorized as treatment success according to Section 13.1.4.1. Imputation will not be performed in the OLE period. Full details will be specified in the Statistical Analysis Plan (SAP).** Added: **The proportion of subjects who experience a 2-grade change from baseline to Week 12 in individual score for roughness and palm/sole assessment will also be explored using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group and the 95% CIs for the differences will be presented.**	To align with current FDA thinking. Single imputation does not consider all missingness patterns. To explore a defined threshold for a clinically meaningful endpoint for phase 3.
Section 13.1.6.1	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) averaged over the BSA.	During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) **for each treated body area (chest/abdomen, back, arms, legs, and face/neck).**	To clarify that all treated areas are included in the local tolerability assessment.

Section	Previous Text	Revision	Rationale
Section 14.7.2	Blood samples will be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed	Blood samples will be used for purposes related to **this study only, and will not be stored for future research**. The samples will be stored until **they are no longer needed**, and the decision has been made that none of the samples needs to be reanalyzed.	To clarify that no samples will be stored for future research

AMENDED PROTOCOL

The following are the amended protocol and appendices, including all revisions specified above.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ATC	anatomical therapeutic chemical
AUC	area-under-the-curve
BMI	body mass index
BSA	body surface area
CFR	code of federal regulations
CI	confidence interval
C_{max}	maximum concentration
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressure
DLQI	dermatology life quality index
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ESS	ectropion severity score
FDA	Food and Drug Administration
GCP	good clinical practice
GEE	generalized estimating equations
HR	heart rate
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IND	investigational new drug
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat

ABBREVIATION	EXPLANATION
IUD	intrauterine device
IWRS	interactive web response system
LI	lamellar ichthyosis
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
MMRM	mixed model of repeated measures
NCA	noncompartmental analysis
OC	observed case
OLE	open-label extension
PG	propylene glycol
PK	Pharmacokinetic(s)
PoC	proof-of-concept
PP	per-protocol
QTc	QT interval corrected for heart rate
RARγ	retinoid acid receptor γ
RBC	red blood count
RR	respiratory rate
RXR	retinoid X receptor
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
TEAE	treatment-emergent adverse event
T_{max}	time of C_{max}
UAE	unexpected adverse event
UADR	unexpected adverse drug reaction
US	United States
UV	ultraviolet
VIIS	Visual Index for Ichthyosis Severity
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of child-bearing potential

5. INTRODUCTION

5.1. Background and Rationale

The ichthyoses comprise a large group of skin scaling disorders with diverse etiology. The stereotypic pathophysiology is epidermal hyperplasia and the formation of excess stratum corneum accompanied by abnormal (delayed and/or disordered) desquamation, with visible accumulation of squames (scales) on the skin's surface – the clinical hallmark of all the ichthyoses.

Lamellar ichthyosis (LI) is recognized as a severe form of ichthyosis that persists throughout life. During the first postnatal weeks, the hyperkeratotic membrane patients are typically born with is gradually shed, and is replaced by scaling and lichenification that involves the entire body including the intertriginous areas, palms, soles, and scalp. While usually not life threatening, LI can result in disability, partial deafness, poor adaptation to environmental conditions (due to hypohydrosis), severe discomfort (pruritus, fissuring of the skin) and significant psychosocial impact.

Lamellar ichthyosis, a member of the nonsyndromic autosomal recessive congenital ichthyosis group of ichthyoses, has an incidence of 1 per 100,000-300,000 live births.[1] Lamellar ichthyosis is undoubtedly a rare disease.

Therapeutic approaches for LI are mainly based on the use of topical emollients, keratolytic agents (urea, lactic acid, salicylic acid), topical retinoids and, in severe cases, oral retinoids.[2,3]

Oral retinoid usage in LI is mainly based on case reports and case series.[4,5,6,7,8] The mechanism of retinoid action involves modulation of keratinocyte differentiation, keratinocyte hyperproliferation and tissue infiltration by inflammatory cells. Systemic retinoids (such as acitretin, etretinate, or isotretinoin) have been found to be efficacious in the treatment of severe ichthyoses, especially in LI.[6]

Vahlquist, et al (2008)[3] report that by combining 2 or more keratolytic agents and moisturizers in the same lipophilic cream base, it is often possible to achieve additive or even synergistic effects in LI without the need to use irritating concentrations of either agent alone. In a double-blind trial of 4 different cream mixtures in 20 patients with LI, a mixture of 5% lactic acid and 20% propylene glycol (PG) in a semi-occlusive cream for 4 weeks twice daily was significantly more effective than 20% PG or 5% urea alone in the same vehicle.[9] Although the treatments were well tolerated, an efficient removal of hyperkeratosis without correcting the underlying biochemical defect in LI is likely to deteriorate the patient's intrinsic barrier problem, because an excessive production of corneocytes probably represents a homeostatic response to an ineffective barrier. Indeed, transepidermal water loss increased after successful treatment of LI with either topical keratolytics[9] or oral retinoid.[10] Although this may not be noticeable by the patient, even minor deteriorations in the barrier function can enhance transcutaneous penetration of active cream ingredients or other topically applied chemicals, which is a matter of special concern in children. Accordingly, α-hydroxy acids and salicylic acid should not be used at all in babies and only with great caution when treating large, eroded skin areas in adult patients.[11,12]

Many patients with LI use pumice, foot files, or gentle rubbing of the skin after a hot bath or a shower to remove scales and hyperkeratosis. Overnight occlusion of problematic skin areas with plastic sheets after applying a thick layer of emollient or keratolytic agents is another way of potentiating therapy, especially on the scalp, which is notoriously difficult to treat. Although

usually effective, all these remedies may further damage the skin barrier and lead to exaggerated epidermal proliferation, erythema, painful erosions and increased transcutaneous penetration.[3]

Based on this information, LI has significant unmet medical need for safer and more effective therapies.

5.1.1 CD5789 (Trifarotene)

CD5789 is a new chemical entity discovered by Galderma R&D SNC and formulated for topical application. It is a novel retinoid acid receptor γ (RARγ) agonist, characterized by its high specificity to this receptor. CD5789 is selective for RARγ over RARα and RARβ (approximately 50- and 8-fold, respectively), with no retinoid X receptor (RXR) activity. CD5789 is currently under clinical development for the topical treatment of various dermatoses, including acne vulgaris and LI.

The pharmacological retinoid-like properties of CD5789 were confirmed in in vitro and in vivo models, showing its interest for its development in the treatment of LI. Therefore, it may have an effect on the differentiation and hyperproliferation of keratinocytes, and consequently improve hyperkeratotic skin of patients with lamellar ichthyosis.

Within the overall acne development program at Galderma, CD5789 has been tested in different pharmaceutical forms for topical administration. As of 15-Jan-2018, 6 different formulations have been evaluated: a solution, a gel and 4 creams (CD5789 cream A, CD5789 cream B, CD5789 cream HE1 concept and its optimized version, cream HE1), with different concentrations (up to 400 µg/g). Therefore, several formulations at different CD5789 concentrations have been tested in nonclinical and clinical development programs.

Galderma decided to develop a new cream formulation that might better address the issue of skin dryness in patients with LI. This formulation was named “Cream HE1 concept.” It has been preliminarily investigated in an exploratory trial in psoriasis at concentrations up to 400 µg/g (RD.03.SRE.40204E). In a proof-of-concept study (RD.03.SRE.40181E), positive results were also obtained in patients with LI with CD5789 cream (up to 100 µg/g) that was effective in decreasing scaling and roughness. Based on these results, a new CD5789 formulation (cream HE1) was developed for further clinical investigations in LI. The formulation cream HE1 was developed with the objective to obtain a formulation with appropriate stability of the active ingredient and in which CD5789 would be homogeneously dissolved in the oily phase at a higher concentration compared to the cream formulation used in the acne program. Cream HE1 contains 100, 200, or 400 µg/g (0.01% [w/w], 0.02% [w/w], 0.04% [w/w], respectively) of CD5789.

Galderma has granted Mayne Pharma LLC an exclusive license to develop and commercialize CD5789 (trifarotene) for LI and other orphan diseases; therefore, the LI indication is no longer pursued by Galderma.

5.2. Clinical Experience

The cream HE1 differs from the CD5789 cream used to treat acne vulgaris in that it contains fewer excipients with drying effects and therefore may be better suited for patients with LI.

Throughout the 30 clinical studies that comprise the clinical development program for CD5789 topical products, 1976 subjects were exposed to CD5789. No systemic safety concerns related to CD5789 gel or creams, or cream HE1 at doses up to 400 µg/g were reported. The subjects were

exposed to a maximal total CD5789 dose of 36 g/day (Investigator's Brochure for CD5789 Cutaneous Formulation).

One study was conducted with CD5789 50 µg/g, 100 µg/g, and placebo in subjects with ichthyosis (Study RD.03.SRE.40181E). Among 31 subjects treated in this study, 17 were treated with CD5789 100 µg/g, and 14 were treated with 50 µg/g (all subjects received placebo [vehicle] on the contralateral zone). Mean (SD) baseline IGA score was 5.7 ± 1.6 among the 31 subjects. Improvement in the investigator's global assessment (IGA) of scaling and roughness was observed by Day 8 with both doses. The primary efficacy criterion was the change in IGA from the Baseline Visit (Day 1) to the Final Visit (Day 43). At Endpoint (intent-to-treat population, last observation carried forward [LOCF]), the CD5789 100 µg/g group had a statistically significant decrease from Baseline in IGA compared with Vehicle (-1.4±2.2; p=0.018) (Investigator's Brochure for CD5789 Cutaneous Formulation).

The CD5789 PK profile was also investigated using cream HE1 (Study GD.03.SRE.103813) in 36 healthy volunteers of Japanese and non-Japanese origin. Subjects were treated daily on up to 90% of body surface area (BSA) for 29 days with up to 36 g of cream formulation. Both CD5789 100 µg/g and 200 µg/g cream HE1 were investigated. Plasma PK assessment demonstrated that repeated topical applications of CD5789 cream HE1 resulted in low and similar CD5789 systemic levels in all treatment groups. In addition, no systemic safety concerns were raised from this healthy volunteer study in which cream HE1 200 µg/g was applied daily under maximal-use conditions on almost the full body. In this study, however, the level of irritation resulted in the need to decrease the frequency of application to twice weekly (Investigator's Brochure for CD5789 Cutaneous Formulation). However, it is possible that absorption in subjects with LI may be greater than in healthy volunteers, due to the skin being compromised.

Based on these data, both the 100 µg/g and 200 µg/g doses showed an acceptable safety profile and will be used in this phase 2 LI study, to determine which of the 2 doses is most effective. The open-label extension (OLE) will evaluate the long-term safety of the higher dose in this patient population.

5.3. Summary of Potential Risks and Benefits

Although the primary objective of this study is safety in the patient population with LI, the potential benefits of study participation are that subjects with LI may experience a reduction in their LI symptoms as a result of treatment with trifarotene (CD5789) cream HE1. No other benefits of participation are anticipated.

The potential risks of study participation for all subjects include those associated with exposure to trifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture. The study population will comprise adults and adolescents aged 12 to 17 years.

Animal studies with CD5789 have shown reproductive toxicity in the embryo-fetal studies. Despite low systemic levels with the CD5789 concentration of 50 µg/g used in patients with acne, CD5789 must not be administered during pregnancy.

When CD5789 is used in the other formulations and/or for other indications and/or with higher concentrations or higher application surface areas, the potential risk of teratogenicity needs to be considered as the safety margin may be lower. Depending on the study population and conditions mentioned above, or other specific requirements, the appropriate contraception method is described in this protocol.

It is unknown whether CD5789 or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Lactating women are not eligible for the clinical study.

Certain cutaneous signs and symptoms of irritation and localized reactions at the application site such as erythema, scaling, dryness, stinging/burning, and pruritus may be experienced with use of CD5789. Depending upon the severity of these side effects, subjects may be instructed to reduce the frequency of application or to discontinue use.

Trifarotene cream contains propylene glycol that is mildly irritant to the skin, eyes, and mucous membranes. Trifarotene (CD5789) cream HE1 also contains butylated hydroxytoluene that may cause local skin reactions (e.g., contact dermatitis), or irritation to the eyes and mucous membranes and sodium benzoate that is mildly irritant to the skin, eyes, and mucous membranes.

CD 5789 is mildly irritant to the skin, eyes, and mucous membranes. Therefore, it should not come into contact with the eyes, mouth, or mucous membranes.

There is a potential risk of skin sensitization. If a reaction suggesting sensitivity to trifarotene (CD5789) cream HE1 occurs, the use of the trifarotene cream HE1 must be discontinued.

There is a potential risk of photosensitivity disorder (sunburn). Excessive exposure to sunlight or ultraviolet (UV) radiation (i.e., occupational exposure to the sun, planned holidays in the sun during the study, phototherapy, tanning salon) must be avoided during the studies. In addition, subjects should take protective measures such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet) and/or seeking shade or shelter from the sun.

As reported with other topical retinoids, there is a potential risk of pigmentation disorders.

No clinically significant systemic risks associated with CD5789 have been identified. Given the mechanism of action for CD5789 Cream HE1, it is assumed that efficacy will increase as the dose is increased. As such, the 200 µg/g dose was selected for the OLE based on its previously established safety profile, expected superiority to placebo and 100 µg/g. However the Data Safety Monitoring Board (DSMB), who will routinely review aggregate safety and tolerability data, as well as any safety concerns brought to the their attention by the study investigators or medical monitor, may determine that the study should be modified, placed on hold, or stopped if serious safety issues are discovered. This is applicable for both the double-blind portion and OLE. If the 200 µg/g dose in raises any safety concerns, the protocol will be amended and the dose will be reduced.

A summary of the pharmaceutical properties and known potential risks of trifarotene (CD5789) cream HE1 is provided in the current version of the investigator brochure (IB). The investigator must become familiar with all sections of the trifarotene (CD5789) cream IB before the start of the study.

6. OBJECTIVES

6.1. Primary Objective

The primary objective is to compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in adults and adolescents with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 12 weeks of treatment.

6.2. Secondary Objectives

The secondary objectives are as follows:

- To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% BSA twice weekly.
- To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.

7. STUDY DESIGN

7.1. Overall Study Design and Plan

The first part of this study is a phase 2, randomized, 2-cohort, double-blind, vehicle-controlled, multicenter study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in adults and adolescents with LI. Adult and adolescent subjects who complete the randomized, double-blind, vehicle-controlled period of the study will be eligible to continue into an open-label extension (OLE) and be treated with trifarotene cream HE1 200 µg/g for an additional 12 weeks.

The randomized, double-blind, vehicle-controlled period of the study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Investigator Global Assessment [IGA] scale where 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe, is designed to compare the safety of 2 doses of trifarotene cream HE1 with that of vehicle in the treatment of LI.

Written informed consent will be obtained from a parent/legal guardian for any minor and minors will provide assent before any study-related procedures are performed.

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods (Table 9-1), as applicable. Washout may be up to 3 months, as necessary.

During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower, but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline. After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.

The first cohort of subjects (Cohort A) will randomize approximately 15 adults (≥18 years old) in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle.

Study drug will be packaged in 50-g tubes from which up to 36 g of IP may be dispensed per application, i.e., the maximum dose per application. Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied (i.e., study staff will measure the 50-g tube before and after the first application to determine the fixed dose amount for each subject). If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.

Thereafter, subjects will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of IP in a tube.

Subjects enrolled in Cohort A will continue treatment for up to 12 weeks.

After the initial 15 subjects complete at least 28 days of treatment, an independent DSMB will review aggregate safety and tolerability data (including PK and electrocardiogram [ECG] data). If

no safety issues are identified, both adults and adolescents (ages 12–17 years, inclusive) will be allowed to enroll in Cohort B (up to approximately 105 subjects). Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and similarly treated twice weekly for up to 12 weeks in the same manner as subjects in Cohort A.

All subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]), any application site reactions, adverse events (AEs), and concomitant medications used. Subjects will also be advised on permitted emollient(s) and/or sunscreen(s) use on nontreatment days during the study; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited.

At all sites with photographic capability photographs will be taken as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional, photographic informed consent form (ICF).

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit, as indicated in the Schedule of Events (Table 2-1). Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application. Subjects should not apply IP on visit days until after the visit.

In addition, a PK substudy will be conducted on Days 1 and 30 at sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 15 adults and 15 adolescents. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for all subjects at specified time points. For the subjects in the PK substudy, postdose ECGs will be performed at each serial blood draw on Day 1 and Day 30.

Efficacy will be assessed by the number of subjects in each treatment group who achieve "success" defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the 5-point IGA scale (i.e., 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe). In addition, efficacy criteria include assessment scales for palm/sole, scaling, roughness, fissuring, and the Dermatology Life Quality Index (DLQI), and the EQ-5D Quality of Life (QoL) Questionnaire. Ectropion Severity Scores (ESS) between the active trifarotene cream HE1 and vehicle groups will be an exploratory endpoint.

Plasma concentrations of CD5789 and its major metabolites will be measured.

Safety will be assessed by evaluating reported adverse events (AEs), changes in clinical laboratory test results, vital sign measurements, physical examinations, 12-lead ECGs, and local tolerability.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent and/or assent through the posttreatment visit) will be documented.

Topical trifarotene cream HE1 was generally well tolerated in recently completed phase 3 pivotal and long-term safety studies in subjects aged 9 years and older with acne vulgaris. The local

tolerability of the trifarotene cream HE1 formulation in subjects with LI is unknown and will be monitored during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) on each treated body area (chest/abdomen, back, legs, arms, and face/neck) and will follow the procedures detailed in Section 9.4.

All subjects (Cohort A and Cohort B) who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for up to 12 weeks. During the OLE, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and Week 24 from all subjects who continue into the OLE (Table 2-2).

Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and AEs; see Section 9.4.

Figure 7-1: Double-blind Study Design

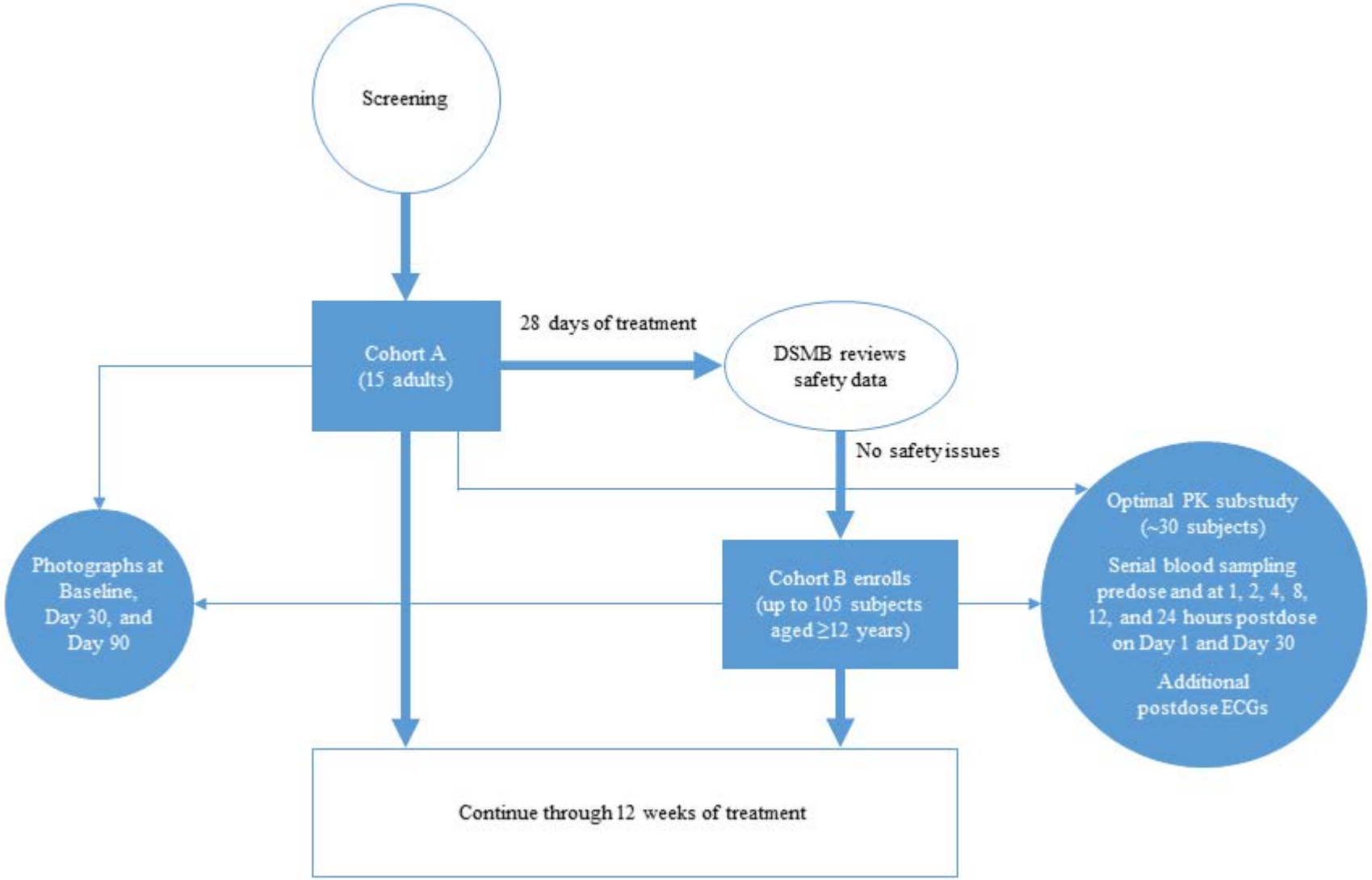
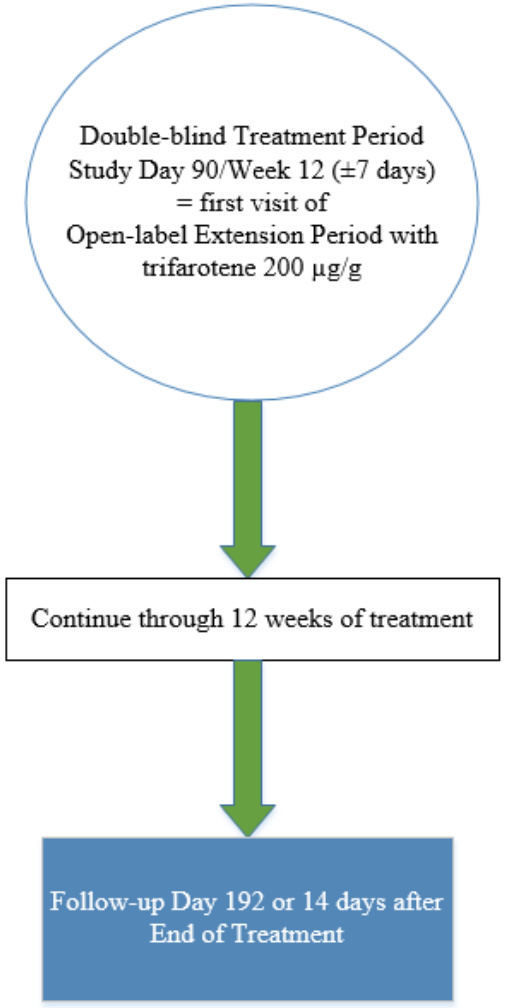


Figure 7-2: Open-label Study Design



7.2. Rationale and Discussion of Study Design

The first part of this study is a randomized, double-blind, placebo-controlled study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in adults and adolescents with LI.

In a previous proof-of-concept study (RD.03.SRE.40181E), subjects with LI applied trifarotene 50 and 100 µg/g cream to limited areas and results demonstrated a decrease in scaling with good safety and tolerance. In a phase 1 study in healthy Japanese and non-Japanese subjects (RD.03.SPR.103813), repeated topical applications of trifarotene (CD5789 cream HE1) 100 µg/g and 200 µg/g resulted in low and similar CD5789 systemic levels in all the cohorts. These studies are fully described in the current Investigational Brochure.

To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of 15 adults randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly. An independent DSMB will review aggregate safety and tolerability data from the initial 15 subjects' first 28 days of treatment. If no safety issues are identified, 105 adults and adolescents (ages 12–17 years, inclusive) will be allowed to enroll in Cohort B and randomized to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly in the same manner as subjects in Cohort A. All subjects in the randomized, double-blind portion of the study will be treated for up to 12 weeks and data on safety, tolerability, PK, and efficacy collected.

Adult and adolescent subjects who successfully complete the initial 12 weeks of double-blind treatment will have the option to enter an OLE with trifarotene cream HE1 200 ug/g twice weekly for up to 12 weeks.

The OLE will collect additional safety, tolerability, PK, and efficacy data. As designed, this study will provide important information on safety, tolerability, and PK with dosing of adolescents and adults with LI for up to 6 months.

The protocol includes appropriate monitoring for safety and tolerability. If subjects develop significant local application site reactions or tolerability issues, the protocol includes language for reducing the frequency of application or halting study drug application until the symptoms abate.

7.3. Selection of Doses in the Study

Based on the results from Study RD.03.SRE.40181E and Study SRE.103813, the doses of 100 µg/g and 200 µg/g were selected for further investigation in adult and adolescent subjects with moderate to severe LI to determine which of the 2 doses is most effective.. The PoC study demonstrated efficacious treatment with 100 µg/g in adults. The PK and tolerability study showed that, when the frequency of application was reduced from daily to twice weekly, the 200 µg/g cream HE1 had good local tolerability.

Therefore, the current study will use these doses compared with vehicle, applied twice weekly on up to approximately 90% BSA in subjects with LI. The OLE will evaluate the long-term safety of the higher dose in this patient population.

7.4. Study Sites

The study will take place at approximately 40 sites in North America, Europe, Israel, and Australia.

7.5. Point of Contact

A point of contact will be identified to provide information to subjects about where to obtain information on the study, the rights of subjects, and whom to contact in case of a study-related injury. This information will be provided in the subject information and informed consent form (ICF).

7.6. End of Study Definition

A clinical trial is considered completed when the last participant's last study visit has occurred.

8. SUBJECT POPULATION

8.1. Selection of Study Population and Diagnosis

Diagnosis of LI for the purposes of this study will be a clinical diagnosis. Although some younger subjects may have had genetic testing, older subjects may not.

While LI is a rare disease and subject enrollment may be challenging, due to possible bias introduced by including household members in the same study, it is recommended that only 1 household member be included in the study to maintain the blind and ensure all assessments are independent.

8.2. Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. For Cohort A: subject is ≥18 years old; for Cohort B: subject is ≥12 years old.
2. Subject has known diagnosis of LI.
3. Subject has moderate to severe (IGA 3–4) LI on the IGA of LI severity.
4. Subject has signed an ICF at Screening before any investigational procedures. Subjects <18 years of age (or Age of Majority) must sign an assent form in conjunction with an ICF signed by the parent/legal representative.
5. Subject who is participating in optional photography has signed a photography ICF.
6. Subject who is participating in the optional PK substudy has signed a PK ICF.
7. Subject is not of childbearing potential, i.e., a female who has not yet begun menstruating or who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason, hysterectomy or bilateral oophorectomy),

   OR

- Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception:
  - bilateral tubal ligation
  - combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline; hormonal contraceptives must inhibit ovulation
  - hormonal intrauterine device (IUD) inserted at least 1 month before Baseline

  OR

  Agrees to abstain from heterosexual intercourse during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study. Abstinence is only acceptable if this is the subject's usual lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

AND

Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application.

Note: Subjects who are premenstrual at Screening but begin menses during the study should follow the pregnancy testing schedule for WOCBP and must abstain from sexual intercourse while in the study and for at least 1 month after the last study drug application.

8. Women of child-bearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine).
9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent/assent, as applicable.
10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

8.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization, including syndromic ichthyoses.
2. Subject has current moderate or severe stinging/burning at Screening.
3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments.
4. Subject with a known lipid disorder (hypertriglyceridemia >200 mg/dL, hypercholesterolemia >250 mg/dL) unless well controlled by stable doses of lipid-lowering agents for at least 6 months.
5. Subject was previously treated with trifarotene/CD5789 in an acne or ichthyosis study.
6. Subject has any other significant concomitant disease, or poorly controlled medical condition other than LI that in the investigator's opinion may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome, Crohn's disease, or ulcerative colitis).
8. Subject is being treated for major depression disorder and/or has a history of major depression or suicide attempt requiring hospitalization, medications, and close psychiatric surveillance to prevent suicide attempts.
9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening.
10. Subject with any of the following laboratory values at Screening:
    a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory
    b. Total bilirubin >1.1 mg/dL or , in case of Gilbert's syndrome, total bilirubin >3 mg/dL
    c. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women
    d. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L.

11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
12. Subject has had recent systemic malignancy (e.g., within 5 years) with exception of nonmelanoma skin cancer or cervical intraepithelial neoplasia of Grade 1 who are >6 months post-treatment.
13. Subject has a history of long QT syndrome or clinically significant ECG abnormalities, including clinically significant conduction disorders or significant arrhythmias, QTcF interval >450 ms, PR interval is not between 120 and 220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed.
14. Subject has a known allergy or sensitivity to any of the components of the investigational products.
15. Subject has been exposed to excessive UV radiations on the treated zones within 1 month before Baseline visit or is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.).
16. Subject is inherently sensitive to sunlight.
17. Subject is unable or unwilling to stop use of topical or systemic retinoids.
18. Subject is presumed to be abusing drug or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms.
19. Subject is participating in another interventional clinical trial.
20. Subject is institutionalized.
21. Subject is in any way related to the sponsor, investigator, or site personnel.

8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

8.4. Discontinuation of Study Intervention

Discontinuation from study treatment does not mean withdrawal from the study, and the remaining study procedures should be completed as indicated in the study protocol (see Section 10.2.4.5). If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

An investigator must discontinue a participant's study treatment for any of the following reasons:

- Pregnancy
- Significant study intervention noncompliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would result in a significant burden to the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for discontinuation of study treatment will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized, and receive the study intervention, and subsequently discontinue study treatment, or are withdrawn from the study will not be replaced.

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.5. Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Randomized subjects withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

9.1. Identification of Investigational Product(s)

Trifarotene cream HE1 is a cream containing 100 or 200 µg/g (0.01% [w/w] or 0.02% [w/w], respectively) of CD5789 and the following excipients: purified water, propylene glycol, allantoin, glycerin, medium-chain triglycerides, polypropylene glycol 15 stearyl ether, cyclomethicone, phenoxyethanol, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane (simulgel 600 PHA), sodium benzoate, butylated hydroxytoluene, and gluconolactone. It is a potent RARγ agonist characterized by its high specificity to this receptor.

Vehicle contains the same ingredients, without the CD5789.

Trifarotene cream HE1 and vehicle will be provided in cream form for topical application and will be supplied in 50-g tubes from which a maximum of 36 g of IP may be extracted,

Trifarotene cream HE1 and vehicle will be supplied by G. Production, Inc. (Galderma) in Baie-D'Urfé, QC, Canada.

9.2. Treatments Administered

For the Double-blind Treatment Period, a fixed dose (determined at Visit 2) of trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject. The IP should be applied thinly and gently rubbed in.

Study staff will apply the first administration of IP in the clinic on Day 1 after Baseline measurements, and the amount of IP used will be measured (i.e., 50-g tube will be measured before and after application to determine amount used). If the product will be applied at home by someone other than the study subject, it is recommended that person assist with application at the first visit to learn how the IP is applied.

The maximum dose per application is 36 g (i.e., 1 tube). Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than full amount of product in a tube. Subjects will continue treatment for up to 12 weeks.

After the Day 1 visit, subjects will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects with heavy facial hair should not apply IP to hair-bearing areas. Persons other than the study subject applying the study drug must wash their hands after application or use disposable vinyl gloves. In addition, a long-handled applicator will be provided for application on the back. The applicator must be washed with warm water and soap after every application.

Trifarotene cream should not come into contact with the eyes, mouth, angles of the nose, or mucous membranes. For the ectropion treatment, Q-tips are recommended for precise application on eyelids, without contact to the eye or conjunctiva. If the IP gets into the eye, it must be flushed immediately with warm water. In case of eye irritation, the subject must be seen by an ophthalmologist.

For the OLE, all subjects will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the Double-blind Period for an additional 12 weeks.

Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained in the skin after the last application.

Subjects should not apply IP on visit days until after the visit, unless they are participating in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the blood draw. Among subjects participating in the PK substudy, ensure the PK line is inserted before study drug application to prevent contamination with the IP and to protect the skin around the needle insertion point from study drug application.

9.3. Selection of Timing of Dose for Each Subject

Subjects will be randomized in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply approximately the same amount of IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week at least 3 days apart on which to apply their IP (e.g., Tuesday and Friday), and maintain that regimen throughout the study. Visits for PK must occur at least 24 hours after the last application of the IP to avoid contamination of the blood samples with any IP that may have remained on the skin after the last application. Subjects should not apply the IP on visit days until after the visit, unless they participate in the PK substudy, in which case the IP will be applied in the clinic on Day 30 after the PK blood draw.

All subjects will be provided with diaries in which to record study drug application (days/times) and any areas of skin not treated (e.g., due to local reactions).

If a subject misses an IP application, they should apply the IP as soon as they remember and record the date/time in the subject diary, then wait at least 3 days and continue their regimen.

Subjects should not shower, bathe, or swim for at least 4 hours after IP application. No occlusive dressings should be used on areas to which IP is applied.

Subjects who continue into the Open-label Extension will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the Double-blind Period for an additional 12 weeks.

9.4. Dose Adjustment Criteria

Local tolerance will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability on a 0-3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) for each treated body area (chest/abdomen, back, arms, legs, and face/neck), and the following procedures will be followed:

- If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area (e.g., the face), the study drug will be applied on this area only once weekly, until the score returns to <2. Continue to treat all other areas twice weekly provided the score is <2 on those areas.
- If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3 (i.e., “drug holiday”). Continue to treat all other areas twice weekly provided the score is <2 on those areas.

Any changes in dosing must be documented in the subject diary and the eCRF.

9.4.1 Stopping Rules

A subject's treatment in either the Double-blind Period or the Open-label Extension must be stopped if any of the following occur:

- Subject becomes pregnant or suspects they are pregnant
- Subject has severe (score of 3) local application site AEs that do not abate with "drug holiday" and reintroduction of IP.
- Subject has clinically significant changes in laboratory values (liver function tests, cholesterol/triglycerides – which may occur with systemic retinoid use)

Any changes in dosing must be documented in the subject diary and the eCRF.

9.5. Treatment Compliance

Subjects will be asked to record their twice-weekly applications of IP in the diary during both the Double-blind Period and the OLE. Deviations from the planned doses (missed dose or timing) will be recorded on the subject's eCRF. Study personnel will review diaries at each visit and diaries will be collected as source documents. Information from subject diaries will be transcribed on the appropriate eCRF pages for documentation of subject compliance with the IP.

Study personnel will assess treatment compliance with IP regimens by weighing IP tubes before dispensing and upon return and by questioning the subject, at every postrandomization visit. A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, supplemented by tube weight. A subject who is not compliant (used 80–120% of IP tubes) will be counseled at each visit on the importance of using the IP as instructed.

Subjects who taper to once-weekly application or who take a "drug holiday" for tolerability will not be reported as having deviated from the protocol (see Section 9.4 for dose adjustment and stopping rules); any changes in dosing must be documented in the subject diary and the eCRF.

9.6. Method of Assigning Subjects to Treatment Groups

In the double-blind, parallel-group, randomized period of the study, subjects who meet study entry criteria will be randomly assigned in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. Study center will not be a blocking factor in the randomization schedule.

Premier Research will prepare the randomization schedule before the start of the study. No one involved in the study performance will have access to the randomization schedule before the official unblinding of treatment assignments. No subject will be randomized into this study more than once.

In the OLE, all subjects will receive trifarotene cream HE1 200 µg/g.

9.7. Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the Double-blind Period of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician and programmer from Premier Research who will have access to the randomization code. The statistician will have access to unblinded data if there is an unblinded DSMB review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

The investigator may discuss with the medical monitor in advance of unblinding a subject, if possible, if it is not deemed an emergency. However, the investigator has the ultimate decision for unblinding a subject for medical treatment and no procedures will prevent or delay necessary unblinding in an emergency for the subject's safety. For emergency unblinding, study personnel will use the IWRS code. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

The primary analysis period is the first 12 weeks of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after database lock has been achieved. A second analysis will take place for endpoints assessed from Week 12 through the OLE.

9.8. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout prohibited topical and systemic treatments with designated washout periods (Table 9-1), as applicable. Washout may be up to 3 months, as necessary.

Table 9-1: Washout Periods for Prohibited Medications

Medication	Washout Period
Topical Treatments	
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	2 weeks
Systemic treatments	
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines (except Vitamin D analogues taken at stable dose since at least 1 month)	8 weeks
QT prolonging drugs	5 half lives
Enzymatic inductors (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (not all inclusive: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives
Monoclonal antibodies (e.g., anti-IL17)	5 half lives

During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower, but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.

After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements.

9.8.1 Permitted Therapies

Subjects will be advised on permitted emollient(s) for use as often as needed on nontreatment days during the study; on treatment days, the use of emollient(s) is permitted except within 4 hours before or after study drug application. Similarly, protective sunscreen should be applied as often as needed, except within 4 hours before or after study drug application. Subjects may use their standard of care treatment on their faces and/or palms/soles after the Week 4 assessment if they experience a worsening of IGA in those areas. In the US/EU, this may include compounded emollients with keratolytics (alpha or beta hydroxyl acids) and/or urea. These standard of care treatments should be approved by the investigator and documented in the eCRF.

Subjects who enter the OLE must stop standard of care treatment. If they experience a worsening of IGA they may use standard of care treatment on their faces and/or palms/soles after the Week 16

visit if the standard of care does not contain prohibited medications. If those standard of care treatments include prohibited medications, the subject should be discontinued from the study.

Other concomitant medications are allowed (e.g., analgesics, antihistamines), but should be limited to those medications considered necessary. All concomitant medications, both prescribed and over-the-counter, should be recorded in the eCRF.

9.8.2 Prohibited Therapies

The medications listed in Table 9-1 are prohibited during the study. Balneotherapy is also prohibited during the Screening Period and during the study.

Subjects may not use concomitant keratolytics such as urea, salicylic acid, alpha, or beta hydroxyacids. Subjects may not use topical or systemic retinoids. Subjects may not take more than 3500 IU/day Vitamin A (e.g., as in a multivitamin). Use of benzoyl peroxide is permitted on nontreatment days for subjects with concomitant acne only); it must not be applied on treatment days due to risk of inactivation of trifarotene by benzoyl peroxide.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continued treatment in the study, at the investigator's discretion with consultation with Mayne Pharma LLC and the medical monitor. For enrolled subjects who require prescription of a systemic azole, the principal investigator should discuss with the medical monitor whether the subject may continue in the study.

9.8.3 Restrictions

Subjects should not shower, bathe, or swim for at least 4 hours after study drug application. No occlusive dressings should be applied to areas where study drug was applied.

Subjects should only use investigator-approved emollients, and should not use them on treatment days within at least 4 hours before and after study drug application.

In addition, subjects should take protective measures to avoid exposure of treated areas to sunlight, such as applying sunscreen (except within 4 hours before and/or 4 hours after study drug application), and/or wearing protective clothing (e.g., long sleeves, hats, and covering legs and feet), and/or seeking shade or shelter from the sun.

9.9. Treatment after End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.10. Dispensing and Storage

The test product supplied by Mayne Pharma LLC is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Premier Research. Until the IP is dispensed to the subjects, it must be stored at 20–25°C (68–77°F), with excursions permitted to 15–30°C (59–86°F); do not freeze and with the tube kept tightly closed in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

9.11. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of subjects (subject number) who received the IP. The investigator will not supply the IP to any person except those named as subinvestigators on the Form Food and Drug Administration (FDA) 1572, designated study personnel, and subjects in this study. The investigator will not dispense the IP from any study sites other than those listed on the Form FDA 1572. Investigational product(s) may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Each subject will be given enough tubes of study drug to apply up to 1 tube-full (approximately 36 g of clinical trial material) per treatment day until the next study visit. Tubes will be packed 2 to a carton, and each subject will receive enough cartons to have the maximum number of tubes needed until the next study visit. The number of study drug tubes the subject needs to provide enough IP until the next visit is shown in Table 9-2.

Table 9-2: Amount of Study Drug Needed Per Visit

Treatment Period	Number of Cartons	Number of Tubes
Double-blind Treatment Period		
Baseline	3	6
Day 14	4	8
Day 30	6	12
Day 60	6	12
OLE		
Day 90	3	6
Day 104	4	8
Day 120	6	12
Day 150	6	12

Each carton will be weighed before dispensing and subjects are to bring all cartons and tubes back at each study visit, whereupon study staff will weigh them again to estimate study drug use and compliance.

Upon completion of the study, the IP (partly used, unused, and empty tubes) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.12. Labeling and Packaging

Labeling and packaging of IP will be performed by Catalent Pharma Solutions, Philadelphia, PA, USA.

Tubes will be packaged in cartons comprising 2 tubes each. Tubes will be labeled with inner and outer booklet labels, and carton number. Each carton will also be labeled with inner and outer booklet labels and numbered.

9.12.1 Labeling

The tubes will have a label affixed that meets the applicable regulatory requirements and may include, but is not limited to, the following: subject identifier, IP name, lot number, protocol number, carton number, caution statement, storage, and sponsor identification.

Save all empty packaging or packaging containing unused tubes for final disposition by the sponsor or contract pharmacy.

Final labeling will comply with the regulatory requirements of each country where the study will be conducted.

9.12.2 Packaging

Investigational products will be packaged in high-density polyethylene, 35×100 mm tubes weighing 50 g from which a maximum of 36 g of IP can be extracted. Trifarotene cream HE1 and vehicle will be packaged so as to be blinded to the investigator, the study clinic personnel, and the subjects.

10. STUDY PROCEDURES

Subjects must provide written informed consent and/or assent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy. Written informed consent will be obtained from a parent/legal guardian for any minor and minors will provide assent before any study-related procedures are performed.

Subjects who agree to participate in the photography and/or PK substudies must provide written informed consent before photographs or serial blood samples are collected.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

10.1.1 Overall Study Schedule

The overall study duration is expected to be approximately 19 months.

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening: up to 35 days (after signing informed consent, if necessary, washout may be up to 3 months, and subjects should return to the site after washout to complete the study eligibility requirements).
2. Double-blind treatment: Twice weekly for 12 weeks.
3. Optional Open-label Extension treatment: Twice weekly for 12 weeks.
4. Follow-up: 14 days after last study drug application.

The maximum treatment duration for each subject is approximately 12 weeks for subjects who choose not to continue into the OLE, and 24 weeks for those who choose to continue.

The maximum study duration for each subject is approximately 229 days (33 weeks).

10.2. Study Periods and Visits

It is suggested that quality of life assessments be conducted first to avoid any bias, and that the IGA be recorded as the first LI assessment at every visit.

10.2.1 Screening and Washout

10.2.1.1 Screening Visit (Visit 1)

The subject must complete eligibility screening within 35 days before randomization in the study. The following procedures will be performed during Screening:

1. Obtain written informed consent and/or assent.
2. Assign a screening number when a subject begins screening.
3. Assess inclusion/exclusion criteria.

4. Collect demographic information.
5. Record medical history, including current therapies (e.g., prescription and nonprescription medications).
6. Perform a physical examination.
7. Measure vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse).
8. Measure height, weight, and calculate body mass index (BMI).
9. Record IGA.
10. Record VIIS.
11. Record roughness assessment.
12. Record palm/sole assessment.
13. Record palm/sole assessment of fissuring.
14. Record ectropion score.
15. Perform a 12-lead ECG.
16. Collect blood and urine for laboratory tests.
17. Perform serum pregnancy test for WOCBP.

Procedures for rescreening subjects who initially fail to meet study entry criteria are described in Section 14.3.

10.2.1.2 Washout

Upon signing informed consent and entering the Screening Period, subjects will stop using physical and medical treatments for LI, including balneotherapy, and may begin to washout the prohibited topical and systemic treatments with designated washout periods, as applicable (Table 9-1). Washout may be up to 3 months, as necessary.

During washout, subjects may continue taking usual care of visible skin (face and scalp) for cosmetic reasons and of extremities (hands and feet) to avoid functional consequences on walking or moving their fingers. Subjects may shower but not bathe or swim. The IGA will be evaluated on the rest of the body at Baseline.

After completing any necessary washout of prohibited medications, subjects will return to the site to complete the study eligibility requirements (Section 10.2.1.1).

10.2.2 Double-blind Treatment Period

Eligible subjects who have washed out prohibited medications will be randomized to double-blind study drug.

10.2.2.1 Baseline Visit (Visit 2, Day 1)

The following procedures will be performed on Day 1 in the study clinic:

1. Review inclusion/exclusion criteria.

2. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.5 and 10.3.1.6 for which version of questionnaire to use).
3. Perform physical examination.
4. Record vital signs (blood pressure and pulse).
5. Record concomitant medications and concomitant therapies.
6. Record IGA.
7. Record VIIS.
8. Record roughness assessment.
9. Record palm/sole assessment.
10. Record palm/sole assessment of fissuring.
11. Record ectropion score.
12. At sites where the photographic substudy is conducted, take photographs of subjects who have provided informed consent for the photography.
13. Perform a 12-lead ECG.
14. Perform urine pregnancy test for WOCBP.
15. Collect blood and urine for routine laboratory tests (subject must be fasting; i.e., at least 8 hours).
16. Randomize via IWRS.
17. Collect a predose PK blood sample (all subjects).
18. Among subjects who consent to participate in the PK substudy, ensure that PK lines are placed before IP application. The IP will be applied in the clinic at this visit, and samples for PK will be taken at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1.
19. Among subjects in the PK study, perform additional ECGs at times of serial sampling.
20. Clinic staff instructs subject on study drug application, applies initial study drug dose and measures amount used (i.e., study staff will weigh the 50-g tube before and after the first application to determine the fixed dose amount for each subject). If the product will be applied at home by someone other than the study subject, it is recommended that person assists with application at this visit to learn how the IP is applied.
21. Assess and record local tolerance/AEs.
22. Dispense study drug and diaries.
23. Advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that at least 24 hours must have elapsed since IP application before their next visit. Subjects should not to apply IP on visit days until after the visit.

10.2.2.2 Telephone Visit (Day 7)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited), and remind subjects that at least 24 hours must have elapsed since IP application before their next visit. Subjects should not apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.2.3 Visit 3 (Day 14 ±5 days)

The following procedures will be performed on Day 14 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.6 and 10.3.1.7 for which version of questionnaire to use).
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Record IGA.
5. Record VIIS~~IGA~~.
6. Record roughness assessment.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring
9. Record ectropion score.
10. Assess local tolerance.
11. Record AEs and review diary.
12. Collect a PK blood sample (all subjects).
13. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
14. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.
15. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.

10.2.2.4 Visit 4 (Day 30 ±7 days)

The following procedures will be performed on Day 30 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.6 and 10.3.1.7 for which version of questionnaire to use).
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Record IGA.
5. Record VIIS.
6. Record roughness assessment.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring
9. Record ectropion score.
10. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
11. Assess local tolerance.
12. Record AEs and review diary.
16. Perform a 12-lead ECG
17. Perform a urine pregnancy test for WOCBP.
18. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
19. Collect a PK blood sample (all subjects).
20. Among subjects who consent to participate in the PK substudy, ensure that PK lines are placed before IP application. The IP will be applied in the clinic at this visit, and samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose.
21. Among subjects in the PK study, perform an additional ECGs at times of serial sampling.
22. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
23. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before and after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.
24. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
25. Provide information about OLE option to study subject.

10.2.2.5 Telephone Visit (Day 45)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited), and remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary. Staff will remind subject about OLE option.

10.2.2.6 Visit 5 (Day 60 ±7 days)

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.6 and 10.3.1.7 for which version of questionnaire to use).
2. Record concomitant medications and concomitant therapies.
3. Record vital signs (blood pressure and pulse).
4. Perform a urine pregnancy test for WOCBP.
5. Record IGA.
6. Record VIIS.
7. Record roughness assessment.
8. Record palm/sole assessment.
9. Record palm/sole assessment of fissuring
10. Record ectropion score.
11. Assess local tolerance.
12. Record AEs and review diary.
13. Collect a PK blood sample (all subjects).
14. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
15. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before and after study drug application is prohibited. Remind subjects that Added reminder that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit..
17. Provide information about OLE option.

10.2.2.7 Visit 6 (90 ±7 days) or Early Termination

The following procedures will be performed on Day 90 in the study clinic:

1. Record responses to DLQI and EQ-5D Quality of Life Questionnaires (see Sections 10.3.1.6 and 10.3.1.7 for which version of questionnaire to use).
2. Perform a physical examination.
3. Record vital signs (blood pressure and pulse).
4. Record concomitant medications and concomitant therapies.
5. Record IGA.
6. Record VIIS.
7. Record roughness assessment.
8. Record palm/sole assessment.
9. Record palm/sole assessment of fissuring.
10. Record ectropion score.
11. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
12. Assess local tolerance.
13. Record AEs and review diary.
14. Perform a 12-lead ECG.
15. Perform a urine pregnancy test for WOCBP.
16. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
17. Collect a PK blood sample (all subjects).
18. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.

For subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 12 weeks of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing, PK from Day 90/Week 12 will be carried over to the OLE and will not be repeated. Subjects will have up to 7 days to decide to enter the OLE; if the subject chooses to continue into OLE, the following additional procedures will be done:

1. Have the subject sign OLE-specific informed consent.
2. Measure subject's weight.
3. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours before or after study drug application is prohibited.

Remind subjects that at least 24 hours must have elapsed since IP application before the PK draws at the Week 16 and Week 24 Visits, and not to apply IP on visit days until after the visits.

4. Weigh new study drug tubes and dispense enough additional study drug until next visit (only for subjects who choose to continue into the OLE).
5. Dispense study diary.

10.2.3 Follow-up Telephone Call (±14 days after Day 90) – Only Subjects Who Do Not Continue into Open-label Extension

Clinic staff will telephone subjects who choose not to continue into the Open-label Extension within 14 days after Day 90 to assess any ongoing AEs.

10.2.4 Open-label Extension

Subjects who successfully complete (i.e., have reliable visit attendance and compliance with IP application, in the investigator's opinion) the initial 12 weeks of double-blind treatment may choose to continue into an optional 12-week OLE with trifarotene cream HE1 200 µg/g. During the OLE, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and 24 from all subjects who continue into the OLE.

10.2.4.1 Telephone Visit (Day 97)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and to remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.2 Visit 7 (Week 14; Day 104 ±5 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.

11. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
12. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit.at the Week 16 and Week 24 Visits, and not to apply IP on visit days until after the visit.

10.2.4.3 Visit 8 (Week 16; Day 120 ±7 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Perform a 12-lead ECG.
11. Perform a urine pregnancy test for WOCBP.
12. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
13. Collect a PK blood sample (all subjects)
14. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
15. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) and/or sunscreen on study drug treatment days within 4 hours before or after study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.

10.2.4.4 Telephone Visit (Day 134)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) and/or sunscreen for use on nontreatment days (use of

emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and to remind subjects that 24 hours must have elapsed since IP application before the subject's next visit. Subjects should not apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.5 Visit 9 (Week 20; Day 150 ±7 days)

The following procedures will be performed at each study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record IGA.
4. Record VIIS.
5. Record assessment of roughness.
6. Record palm/sole assessment.
7. Record palm/sole assessment of fissuring.
8. Record ectropion score.
9. Assess and record local tolerance/AEs and review diary.
10. Perform a urine pregnancy test for WOCBP.
11. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
12. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.

10.2.4.6 Visit 10 (Week 24; Day 180 ±7 days) or Early Termination

The following procedures will be performed at Week 24 in the study clinic:

1. Perform a physical examination.
2. Record vital signs (blood pressure and pulse).
3. Record concomitant medications and concomitant therapies.
4. Record IGA.
5. Record VIIS.
6. Assess roughness.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring.
9. Record ectropion score.
10. Assess local tolerance
11. Record AEs and review diary.

12. Perform a 12-lead ECG.
13. Perform a urine pregnancy test for WOCBP.
14. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
15. Collect a PK blood sample (all subjects)
16. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.

10.2.4.7 Follow-up Evaluation – Open-Label Extension (Week 26/Visit 11)

At 14 days after the last administration of the IP, the following procedures will be performed:

1. Perform a physical examination.
2. Record vital signs (blood pressure and pulse).
3. Record any concomitant medications/therapies.
4. Record IGA.
5. Record VIIS.
6. Assess roughness.
7. Record palm/sole assessment.
8. Record palm/sole assessment of fissuring.
9. Record ectropion score.
10. Assess and record AEs occurring since the last evaluation and review diary.
11. Perform a urine pregnancy test for WOCBP.

10.3. Assessments

The 5-point IGA is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. The IGA scale was developed with the support of experts from academic reference centers for the treatment of ichthyosis. Each level of severity will consider both the severity of scaling and the severity of roughness (Section 10.3.1.2). While retinoid treatment is expected to reduce scale, it may increase erythema; therefore, in this study, erythema will be evaluated as part of local tolerability.

10.3.1 Efficacy Variables

All efficacy measurements will use scales previously used for dermatological studies or as defined in the following sections.

10.3.1.1 Investigator's Global Assessment

The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear and at least a 2-grade change from Baseline at Week 12/EOT in the Double-blind Period on a 5-point IGA full body scale.

The investigator will rate the subject's condition using the 5-point IGA at each time point shown in the Schedule of Events (Section 2.2).

The IGA will be measured on a 5-point scale, excluding the following areas: knees, elbows, neck, palms, soles, axillae, groin, and scalp:

0	Clear	No scaling and no roughness
1	Almost Clear	Occasional fine scales; hardly palpable roughness (mostly smooth)
2	Mild	Small and fine scales predominate; no more than a few large scales; mild roughness on palpation
3	Moderate	Some large scales that may be thick,; coarse roughness on palpation
4	Severe	Confluent, primarily large (>1 cm), thick scales with plate-like hyperkeratosis

10.3.1.2 Visual Index for Ichthyosis Severity – Scaling

The secondary endpoint is the number of subjects in each treatment group who experience a severity score of 0 or 1 at Week 12/EOT on the overall 16-point VIIS for scaling.

The investigator will rate the subject's condition using the 5-point VIIS for each body area (chest/abdomen, back, legs, and arms) and an overall score at each time point shown in the Schedule of Events (Section 2.2):

0	Normal skin; no perceptible scale or smoothening
1	Areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
2	Confluent smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
3	Confluent scales (visibly separated/fractured stratum corneum) including some large (>1 cm), thick scales
4	Confluent, primarily large, thick scales

10.3.1.3 Individual Score for Roughness

The amount of roughness of the skin overall will be measured on a 5-point scale.

0	Clear	Smooth skin
1	Almost Clear	Hardly palpable roughness
2	Mild	Mild roughness (fine sand paper-like)
3	Moderate	Moderate, coarse roughness (coarse sand paper-like)

4	Severe	Very coarse skin (broken cornflakes-like)

10.3.1.4 Palm/Sole Assessment

Thickening of the skin on the palms and soles will be measured on a 5-point scale.

0	Clear	No thickening, no roughness, no fissure
1	Almost Clear	Only slight thickening, minimal to no roughness, no fissures
2	Mild	Some thickening, mild roughness on palpation, few fissures may be present
3	Moderate	Substantial and diffuse thickening, coarse roughness on palpation may be present, fissures may be present
4	Severe	Very thickened and rough skin, numerous fissures

10.3.1.5 Palm/Sole Fissuring Assessment

Fissuring will be assessed by recording the presence or absence of fissures, the number of fissures present, and the pain associated with each fissure. A fissure is a longitudinal and deep crack that separates the stratum corneum and may penetrate down to the dermis, causing pain and sometimes bleeding. The subject will assess pain associated with fissures as ranging from 0-3 (none, mild, moderate, severe).

10.3.1.6 Dermatology Life Quality Index

The DLQI is a dermatology-specific Quality of Life instrument for subjects aged 17 years and older (1992). The child DLQI (cDLQI; May 1993) is for subjects aged 12 to 16 years. It is a simple 10-question validated questionnaire with 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment); higher scores indicate poorer quality of life. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The investigator should use his or her judgment of the maturity of the subject to decide which version of the questionnaire to use; the same version must be used for the subject throughout the study.

10.3.1.7 EQ-5D Quality of Life Questionnaires

The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS). The EQ-5D-5L (2009) is intended for use in adult subjects, while the EQ-5D-Y (2012) is to be used for children and adolescents. The investigator should use his or her judgment of the maturity of the subject to decide which version of the EQ-5D to use; the same version must be used for the subject throughout the study.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the subject's self-rated health on a

vertical 0-100 VAS. This can be used as a quantitative measure of health outcome that reflects the subject's own judgement.

10.3.1.8 Ectropion Severity Score

The Ectropion Severity Score (ESS), has a maximum score of 8 points. A higher score indicates a worse ectropion. The score takes the severity of ectropion in terms of lateral and medial apposition, scleral show, conjunctival show, and roundness of the eye into account and gives an indication of the functional aspects involved in ectropion by scoring redness, excess tear film, and the position of the lacrimal punctum.[14]

	Points per Item		
	0	0.5	1
Lateral apposition	Nonaffected	—	Affected
Medial apposition	Nonaffected	—	Affected
Sceral show	No	≤1 mm	>1 mm
Conjunctival show	No	—	Yes
Excess tear film	No	—	Yes
Redness of the eye	No	—	Yes
Round canthus	No	—	Yes
Punctum lacrimale	Invisible	Emerging	Visible
Maximum score			8 points

Figure 10-1: Ectropion Severity Score

Source: Korteweg SFS, Stenekes MW, van Zyl FE, Werker PMN. Paralytic Ectropion treatment with lateral periosteal flap canthoplasty and introduction of the ectropion severity score. *Plast Reconstr Surg Glob Open.* 2014;2(5):e151.

10.3.1.9 Photography Substudy

All sites that have photographic capability will take photographs as source data to support scoring at Baseline, Day 30, and Day 90. A central reader who will not be an investigator in the study will review the photographs to assess consistency of investigator scoring of LI severity as a quality check. Photographs may also be used for scientific publication purposes. Subjects will sign a separate, optional photographic informed consent form (ICF).

10.3.2 Clinical Pharmacology

10.3.2.1 Pharmacokinetic Analysis Methods

The pharmacokinetic characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis (NCA).

10.3.2.2 Pharmacokinetic Parameters

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit for trough values.

Subjects who provide written informed consent to participate in the optional PK substudy will provide blood samples for PK analysis predose on Day 1 and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30.

The PK parameter estimates will be completed using WinNonlin (Pharsight Corporation) software using the actual elapsed times from dose administration to sample collection (i.e., not nominal time).

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the maximum concentration (C_{max}) and the time of C_{max} (T_{max}). Additional details of the parameters and their calculation and evaluation will be included in the statistical analysis plan (SAP).

Table 10-1 shows the PK parameters that will be computed for each subject for samples obtained over the planned sampling intervals.

Table 10-1: Pharmacokinetic Parameters

Parameter	Description of Parameter
C_{max}	Maximum (or peak) serum concentration
T_{max}	Time at which C_{max} is observed
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration
$AUC_{(0-inf)}$	Area under the plasma concentration-time curve from time 0 to infinity (if data permits)
$t_{1/2}$	Apparent first order terminal elimination half-life
λ_z	Apparent terminal phase rate constant (if data permits)

10.3.3 Sample Collection

Samples will be collected at the time points specified in the Schedule of Events (Section 2.2). Specimen preparation, handling, shipment, and storage for the complete blood count, chemistry, and urinalysis are described in the study laboratory manual. Finding veins in subjects with this disease can be challenging. Blood draws will be done at the corresponding study visits before application of the IP and should be 24 hours after IP application. Subjects must not apply the IP to the area where blood will be drawn within 24 hours before their next study visit to avoid contamination of the blood by IP that remained in the skin. For subjects in the PK substudy, a cannula should be placed before IP application and the cannula site may be occluded to prevent contamination with IP.

Actual PK sample times for subjects in the PK substudy will be recorded in the eCRF.

Blood

For subjects not in PK substudy:

The expected amount of blood to be drawn at each visit varies from approximately 6 mL to a maximum of 21 mL (Screening Visit only). The total amount of blood drawn for the study will be about 123 mL per subject, unless the subject takes part in the PK substudy.

For subjects in PK substudy:

For subjects who opt to participate in the PK substudy, extra blood samples will be drawn at Visit 2 and at Visit 4 for PK analysis. The amount of blood to be drawn per subject at each of these visits will be approximately 54 mL. For subjects taking part in the substudy, the total amount of blood drawn for the entire study will be approximately 195 mL.

Urine

Urinalysis will be performed at central laboratory. Dipstick and urine pregnancy tests will be conducted on site.

10.3.4 Safety Variables

Safety assessments will include the evaluation of AEs, including local tolerability (stinging/burning, pruritus, and erythema), clinical laboratory assessments, vital signs, 12-lead ECGs, and physical examinations.

10.3.4.1 Clinical Laboratory Safety Assessments

10.3.4.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 2.2).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides
Coagulation Panel:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones
Pregnancy Test:	for women of childbearing potential only; serum at Screening, urine at each other visit.
Serology	Hepatitis B surface antigen, and hepatitis C

All blood samples for the clinical laboratory tests must be taken in a fasting state, at least 8 hours after the previous drug application.

Blood and urine samples for hematology, and serum chemistry will be sent to a central laboratory for analysis. Urine pregnancy tests and dipstick will be conducted at the study sites.

10.3.4.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

Samples for assessment of clinical laboratory tests will be transported to the Clinical Reference Laboratory (see the study laboratory manual for addresses).

10.3.4.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Mayne Pharma LLC prior to beginning the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically significant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical significance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically significant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.4.2 Clinical Examinations

10.3.4.2.1 Vital Signs

Vital signs, including height and weight (only assessed at Screening), blood pressure, and pulse will be measured.

10.3.4.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. All ECG recordings will be identified with the subject number, date, and time of the recording. Gel ECG electrodes may be used for ECGs because they are more conductive and cause less trauma on compromised skin. Efficacy assessments should be conducted before ECGs to avoid possible artefact/changes from the ECG.

For subjects in the PK substudy, additional ECGs will be performed postdose during serial blood sampling on Day 1 and Day 30.

If there is a marked prolongation of the QT/QTc interval during treatment, a subject should be discontinued from the IP but remain in the study until full resolution of the event. The DSMB will be informed immediately of such an occurrence.

10.3.4.2.3 Physical Examination

A complete physical examination excluding the genitourinary examination will be performed at Screening, while limited physical examinations (to include HEENT, cardiorespiratory, abdomen, and range of motion) will be performed as indicated in the Schedule of Events (Section 2.2).

10.3.4.2.4 Other Safety Variables

Local tolerability will be assessed on a 0-3 scale (none, mild, moderate, severe). All application site reactions will be recorded as TEAEs in the diary. These should include the date and severity of the TEAE.

10.3.4.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in subjects treated with control product are also considered AEs.

11.1.2 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADRs).

The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IP qualify as ADRs.

All AEs for which the judgment of relationship to IP is "possible" or higher will be considered ADRs. If a relationship to IP is not provided, then the AE must be treated as if it were "possible."

11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For a preapproval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure [IB] for an unapproved investigational product or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events.

11.1.4 Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first application of IP (trifarotene or vehicle) and not more than 14 days after the last application of IP.

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review by a study monitor.

All reported AEs, including local and systemic AEs not meeting the criteria for SAEs, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All reported AEs occurring while on study must be documented appropriately regardless of relationship. All reported AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of a reported AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study clinic personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 14 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs. In addition, although local tolerability will be assessed on a 0-3 scale, all application site reactions should be recorded as AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as follows:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3 Action(s) Taken

All AEs will be treated/managed according to standard practice. The following actions may be taken with regard to the IP. Section 9.4 describes dose adjustment and stopping rules for individual subjects.

Action(s) taken may consist of the following:

Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome of an AE at the time of last observation will be classified as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to IP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related	An AE with a reasonable time sequence to administration of the IP, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Related	An AE occurring in a causal plausible time relationship to IP administration that cannot be attributed to a concurrent disease or other drugs, chemicals, or events. The AE relationship to the IP must be assessed separately by the investigator and Mayne Pharma LLC.

11.2.3 Documentation

Any AE that occurs during the Screening Period will be captured as on the AE page of the eCRF (not medical history). All AEs that occur within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP(s)

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject may be withdrawn for treatment but continue to be followed for efficacy and safety in the study. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

It is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

Any AE will be followed (up to a maximum of 14 days after the last dose of IP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to Premier Research within 24 hours of first becoming aware of the event by e.g., completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the Premier Research by one of the following methods:

Email: globalPV-US@premier-research.com

Email: PVDS-ROW@premier-research.com

Fax number: +1 215 972 8765

Fax number: +421 2 6820 3713

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of IP(s)
- Date of last dose of IP(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s) ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, adverse event, date of occurrence, subject identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the Premier Research Pharmacovigilance Department using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB)/independent ethics committee (IEC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.2 Adverse Drug Reactions

All ADRs should be reported by the investigator in the eCRF.

Suspected serious ADRs must be reported to the sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.3 Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported by Premier Research to Mayne Pharma LLC in aggregate monthly status reports.

11.3. Special Considerations

11.3.1 Adverse Events of Special Interest

Since topical retinoids are associated with local application site AEs, particularly when beginning treatment, these events will be followed closely during the study and considered AEs of special interest (AESIs).

11.3.2 Pregnancy

All WOCBP who participate in the study should be counseled on the need to practice highly effective birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during IP treatment will be immediately discontinued from study treatment. The investigator must report the pregnancy of any woman who becomes pregnant during or within 30 days after discontinuing treatment as if it were an SAE within 24 hours of learning of the pregnancy, to Premier Research Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The

investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an SAE and AE form (entering the event temporarily as nonserious on both forms) provided by the sponsor or its designee. If a partner of a male study subject becomes pregnant, the investigator must report the pregnancy as soon as possible after learning of it to the Premier Research Pharmacovigilance using the Pregnancy Data Collection Form. A separate pregnant partner ICF will be required.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy in a study subject. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

Among the clinical studies, 12 pregnancies were reported: 4 resulted in normal births; 5 resulted in spontaneous abortions (none of which was considered related to CD5789); 1 was electively aborted, and 2 were lost to follow-up (Investigator's Brochure for CD5789 Cutaneous Formulation).

12. DATA SAFETY MONITORING BOARD

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including LI. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate under a charter that will be finalized prior to the start of the study. The DSMB will meet at least 3 times during the conduct of the study: when the study begins, when 15 adult subjects have enrolled in Cohort A and have completed at least 28 days of treatment, and after 60 subjects have enrolled in the study.

The DSMB will meet after 15 subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data (including PK and ECG results). The safety data will be unblinded. At that time, the DSMB will decide whether Cohort B (adults and subjects aged 12–17) may begin enrolling, or if additional adult safety data are required before allowing subjects aged 12 – 17 to participate in the study. The DSMB will have the authority to recommend to the sponsor that the study be modified, placed on hold, or stopped if serious safety issues are discovered. The DSMB will provide its input to Mayne Pharma LLC. Any protocol changes the DSMB may suggest will be submitted to all applicable regulatory bodies for review and approval.

In case of significant toxicity, the DSMB may choose to review the available safety data and recommend stopping recruitment in a particular dose group.

Stopping rules for individual subjects are in Section 9.4.1.

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. A SAP that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a P value of ≤ 0.05 will be considered statistically significant.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will include the number and percentage of subjects in each category.

The primary analysis period is the first 12 weeks of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after the database is locked. A second analysis will take place for endpoints assessed from Week 12 through the OLE Period. The baseline for the safety and efficacy parameters will be measured at Visit 1 or Visit 2, per the Schedule of Events for both the Double-blind Period (Table 2-1) and OLE (Table 2-2).

13.1.1 Analysis Populations

The following 5 analysis populations are planned for the Double-blind Period of this study:

- Safety: all subjects who are randomized to treatment and receive at least 1 application of study drug in the Double-blind Period. This population will be the primary population for analyses of safety.
- Intent-to-treat (ITT): all randomized subjects. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study.
- Modified intent-to-treat (mITT): all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period.
- Per-protocol (PP): subjects in the mITT Population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations.
- Pharmacokinetic: all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. This population will be used to summarize all PK endpoints.

The following analysis populations are planned for the OLE of this study:

- OLE Safety: all subjects who complete the 12-week Double-blind Treatment Period and receive at least 1 application of study drug in the OLE.
- OLE ITT: all subjects who complete the 12-week Double-blind Treatment Period and sign the OLE informed consent.
- OLE mITT: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6.

- OLE PP: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study.

Inclusion in the analysis populations will be determined prior to database lock.

If a subject is randomized incorrectly or is administered the incorrect IP, analyses of the ITT and mITT populations will be based on the assigned treatment whereas all other analyses will be based on the actual treatment received.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

For the Double-blind Period, the numbers of subjects randomized, completing Week 12 of the study, and withdrawing early from the Double-blind Period, along with reasons for withdrawal, will be tabulated overall and by randomized treatment group. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated by randomized treatment group. This analysis will be conducted for the ITT population.

For the OLE, the number of subjects entering the OLE, completing the study, and withdrawing early, along with reasons for withdrawal, will be tabulated overall. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated. This analysis will be conducted for the OLE ITT population.

13.1.2.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations promptly. All deviations must be addressed in study source documents, and reported to Premier Research or Mayne Pharma LLC. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

Subjects who taper to once-weekly application or who take a “drug holiday” will not be reported as having deviated from the protocol.

13.1.2.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for the ITT and OLE ITT populations.

Demographic variables will include age, sex, race, ethnicity, height, weight, and BMI. Baseline subject characteristics will include medical history, physical examination findings, and IGA score.

Prior and concomitant medications will be summarized by randomized treatment group, by the number and percentage of subjects taking each medication, and classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of each subject's dose, and in terms of duration of exposure for each period. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group. Additionally, the number of subjects who are compliant with investigational product will be presented by treatment group for the Double-blind Period and overall for the OLE.

Subjects who taper to once-weekly application or who take a "drug holiday" will not be reported as having deviated from the protocol.

13.1.4 Efficacy Analysis

The ITT population will be used as the primary population for the primary analysis of efficacy at Week 12. Select efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE using the OLE ITT, OLE mITT, and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE.

13.1.4.1 Efficacy Endpoints

Primary efficacy endpoint: The proportion of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 2-grade change from Baseline at Week 12/EOT in the Double-blind Period on the 5-point IGA scale.

Secondary: The secondary endpoints are as follow:

- The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices from Baseline through Week 12:
  - 5-point VIIS scale for scaling from Baseline through Week 12
  - Individual score for roughness (Scale: 0–4) overall
  - Palm/sole Assessment (Scale: 0–4)
  - Quality of life per DLQI and cDLQI
- The difference in proportion of subjects with presence of fissures on palm/soles (presence/absence, number of fissures, and pain associated with fissures [on a 0-3 scale]) at Week 12 between the active trifarotene cream HE1 and vehicle groups

Exploratory: The exploratory endpoints are as follow:

- The difference in mean ectropion scores (ESS of 0–8) between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12
- The difference in quality of life per EQ-5D-5L and EQ-5D-Y scores between the active trifarotene cream HE1 and vehicle groups from Baseline through Week 12

13.1.4.2 Primary Analysis

For the Double-blind Period only, the number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT will be presented. The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group, 95% CIs for the differences, and P-values for the differences in treatment will also be presented.

Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from baseline will be provided for IGA scores for both periods.

13.1.4.3 Secondary Analyses

Secondary and exploratory efficacy endpoints will be analyzed separately for each period (Double-blind and OLE) using descriptive statistics.

Additionally, for the Double-blind Period only, change from Baseline in continuous secondary endpoints through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate.

For subjects who report having fissures, descriptive summaries of the number of fissures and pain related to fissures will also be presented by treatment group and body area for each period.

The DLQI scores will also be analyzed using descriptive statistics through Week 12.

The proportion of subjects with at least a 50% reduction in IGA score from Baseline will be analyzed using the same logistic regression analysis described in Section 13.1.4.2.

13.1.4.4 Exploratory Analyses

Descriptive summaries and the changes from baseline will be provided for ectropion scores and EQ-5D-5L scores by visit for each period. No formal inferential analyses will be conducted for exploratory endpoints.

13.1.4.5 Corroborative, Sensitivity, and Other Analyses

To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using multiple imputation (MI) for the Double-blind Period only. Multiple-imputations will be used to replace missing IGA outcomes using multiple draws from the posterior predictive

distribution estimated from the treatment groups. IGA scores will be imputed and then categorized as treatment success according to Section 13.1.4.1. Imputation will not be performed for the OLE. Full details will be specified in the SAP.

The proportion of subjects who experience a 2-grade change from baseline to Week 12 in individual score for roughness and palm/sole assessment will also be explored using a logistic regression model with treatment and age group as factors. Other baseline characteristics and interactions may be included. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI and vehicle cream group and the 95% CIs for the differences will be presented.

For analyses involving study site, if the number of subjects per site is small, sites may be pooled for safety and efficacy analysis or omitted from statistical models as the anticipated number of subjects per site is small, treatment is self-administered, and the sites are using standardized procedures for all assessments. If the distribution of enrollments at sites is such that one or few are enrolling a majority of subjects, a subgroup analysis by site may be performed. The final determination will be made prior to database lock.

Details of these analyses will be further detailed in the SAP.

13.1.5 Clinical Pharmacology Analyses

13.1.5.1 Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics. Descriptive statistics reported will include the arithmetic mean, SD, CV%, geometric mean, minimum, maximum, and median. Only the range and the median will be reported for T_{max}, as this is a categorical parameter. The PK parameters will also be summarized by treatment using descriptive statistics.

Individual plasma concentration plots and mean data graphs will be produced using both linear and semi-logarithmic scales. Mean data graphs will show plasma concentration profiles by treatment group.

Pharmacokinetic plasma parameter estimates and summaries will be completed for the subjects in the PK population. Testing of PK parameters will be outlined in the SAP.

13.1.6 Safety and Tolerability Analyses

Safety analyses through Week 12 of the Double-blind Period will be conducted using data from the Safety Population and safety analyses in the OLE will be conducted using the OLE Safety Population (as defined in Section 13.1.1). Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, and physical examination results. No formal inferential analyses will be conducted for safety variables in either period.

13.1.6.1 Local Tolerability

During all clinic visits, the investigator will assess local tolerability (Scale: 0-3 [none, mild, moderate, severe]) for each treated body area (chest/abdomen, back, arms, legs, and face/neck). Descriptive summaries will be presented by period, treatment group, and visit.

13.1.6.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1 or higher.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first, or
- AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first.

The number and percentage of subjects with AEs will be displayed by each treatment group in the Double-blind Period and overall in the OLE by system organ class and preferred term. Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.6.3 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each treatment group at each time point in each period.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory parameter by treatment group and by study visit in each period.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.1.6.4 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse for each period.

The number of subjects with vital signs values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each parameter by period, by treatment group and by study visit. Pre and post-treatment values may also be presented with an analysis of mean changes from baseline.

13.1.6.5 Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point in each period. Abnormal results will be grouped as clinically significant and not clinically significant.

A comparison of QT results will be presented. Summary statistics will be displayed by period, by treatment group, and by visit for QT and the QT interval corrected for heart rate (QTc) calculated using Fridericia's QT correction methods.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTcF interval (Fredericia's correction methods), and HR for each treatment group at each time point in each period.

13.1.6.6 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group in each period.

13.1.7 Interim Analysis

No interim analyses are planned.

13.2. Sample Size Determination

Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) 2-sided Fisher's Exact Test assuming a 70% success rate and a 40% success rate, respectively. This study is not powered to detect a difference between the 2 active arms.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Mayne Pharma LLC agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with ICH GCP, and the applicable United States (US) Code of Federal Regulations (CFR). The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IP(s), and their specific duties within the context of the study. Investigators are responsible for providing Mayne Pharma LLC with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all

documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Premier Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Premier Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Premier Research

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory/GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening Visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4. Study Documents

All documentation and material provided by Mayne Pharma LLC for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Consent and assent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The informed consent and assent forms are submitted with this protocol.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent and assent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent and assent forms and ask questions before signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate. The participant will sign the informed consent or assent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent and assent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory/Good Clinical Practice Documents

The regulatory/GCP documents are listed below.

- Signed original protocol (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and subinvestigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form Signature Log/Delegation of Study-related Duties
- Approved ICF and subject materials
- FDA1572 and financial disclosure forms, as applicable (US sites)
- Any other relevant GCP documents

The regulatory/GCP documents must be received from the investigator and reviewed and approved by Mayne Pharma LLC or its designee before the study site can initiate the study and before Mayne Pharma LLC will authorize shipment of IP to the study site. Copies of the investigator's regulatory/GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the trifarotene (CD5789) Cream IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and IP accountability records should also be retained as part of the investigator's regulatory/GCP documents. It is the investigator's responsibility to ensure that

copies of all required regulatory/GCP documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.5. Data Quality Control

Mayne Pharma LLC and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

Mayne Pharma LLC and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Mayne Pharma LLC personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures

- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF will be provided to the sites. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Mayne Pharma LLC or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan (CMP).

14.5.2 Data Management

Mayne Pharma LLC or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data management plan (DMP) will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries will be provided to the sites.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Mayne Pharma LLC or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or clinical study report [CSR])

Mayne Pharma LLC or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Mayne Pharma LLC immediately.

14.6. Study Termination

The study may be terminated at Mayne Pharma LLC's discretion at any time and for any reason.

The DSMB may recommend discontinuation of the study if they find evidence of unacceptable risk to subjects.

14.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, Mayne Pharma LLC or designee will notify the IECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

14.6.2 Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by Mayne Pharma LLC, IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Mayne Pharma LLC or its designee will notify the IECs and regulatory authorities about the premature termination as required according to national laws and regulations. Mayne Pharma LLC or its designee must clearly explain the reasons for premature termination.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the IND or IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is terminated prematurely, all investigators have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Follow-up Visit.

The study might resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or FDA.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. Mayne Pharma LLC may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1 Record Retention

For sites in the US, the investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until 1 of the following occurs:

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

Outside of the US, after completing the study, Mayne Pharma LLC will receive the original eCRFs or at least a legible copy and retain the documents for at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

14.7.2 Sample Retention

Blood samples will be used for purposes related to this study only, and will not be stored for future research. The samples will be stored until they are no longer needed, and the decision has been

made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

Data collected for this study will be analyzed and stored at Premier Research.

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Mayne Pharma LLC. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9. Use of Information and Publication

All information concerning trifarotene (CD5789) cream HE1, Mayne Pharma LLC's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Mayne Pharma LLC or its designee to the investigator, and not previously published, is considered confidential and remains the sole property of Mayne Pharma LLC. Case report forms also remain the property of Mayne Pharma LLC. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by Mayne Pharma LLC in connection with the continued development of trifarotene (CD5789) cream HE1 and thus, may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Mayne Pharma LLC. Publication or other public presentation of trifarotene (CD5789) cream HE1 data resulting from this study requires prior review and written approval of Mayne Pharma LLC. Abstracts, manuscripts, and presentation materials should be provided to Mayne Pharma LLC for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until Mayne Pharma LLC has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

15. FINAL CLINICAL STUDY REPORT

Mayne Pharma LLC will retain ownership of the data.

The final CSR will be written within 1 year of completion of the clinical part of the study. For pediatric studies, the final CSR will be written within 6 months. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

16.2. Subject Information and Informed Consent and/or Assent

A properly constituted, valid IRB or IEC must review and approve the protocol, the investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent and/or assent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed assent or consent prior to enrollment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent and/or assent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Mayne Pharma LLC, and/or the sponsor's designee. Collection of informed consent and/or assent has to be documented in the eCRF.

Furthermore, the subject will be informed that if he or she wishes to dropout or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory

authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

16.3. Approval by Institutional Review Board and Independent Ethics Committee

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's or the sponsor's representative before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must follow local country requirements.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by Mayne Pharma LLC before implementation.

16.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

17. REFERENCES

1. Vahlquist A, Blockhuys S, Steijlen P, et al. Oral liarozole in the treatment of patients with moderate/severe lamellar ichthyosis: results of a randomized, double-blind, multinational, placebo-controlled phase II/III trial. *Br J Derm*. 2014;170(1):173-181.
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3. Vahlquist A, Gånemo A, Virtanen M. Congenital ichthyosis: an overview of current and emerging therapies. *Acta Derm Venereol.* 2008;88(1):4–14.
4. Blanchet-Bardon C, Nazzaro V, Rognin C, Geiger JM, Puissant A. Acitretin in the treatment of severe disorders of keratinization. *J Am Acad Dermatol.* 1991;24(6):982–986.
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12. Chiaretti A, Wismayer DS, Tortorolo L, Piastra M, Polidori G. Salicylate intoxication using a skin ointment. *Acta Paediatr*. 1997;86(3):330-331.
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18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER: 18-ICH-001

PROTOCOL TITLE: A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale

AMENDMENT 1 DATE: 28-Jun-2019

The undersigned acknowledges possession of and has read the product information (e.g., investigator's brochure) on the IP and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected subjects in his/her care, according to the study protocol.

He or she agrees to use the study material, including IP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Mayne Pharma LLC.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Mayne Pharma LLC within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IP.

He or she agrees to comply with Mayne Pharma LLC and regulatory requirements for the monitoring and auditing of this study. In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

APPENDICES

A. Regulations and Good Clinical Practice Guidelines

A. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives (and applicable regulations/guidances):

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents>

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf

PROTOCOL/CLINICAL INVESTIGATION PLAN

PRODUCT NAME/NUMBER:	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER:	18-ICH-001
IND NUMBER:	<IND Number>
NCT NUMBER:	NCT03738800
EUDRACT NUMBER:	2018-003272-12
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	A Phase 2 Randomized, Multicenter, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale
PROTOCOL DATE:	Final v1.0, 28-Nov-2018
COORDINATING/PRINCIPAL INVESTIGATOR:	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine, PO Box 208059 333 Cedar Street New Haven, CT 06520, USA phone: +1 203 789 1249
SPONSORED BY:	Mayne Pharma LLC 1240 Sugg Parkway Greenville, NC 27834, USA +1 984 242 1400
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive, Suite 150 Durham, NC 27709, USA +1 919 627 9100

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: 18-ICH-001

PROTOCOL TITLE: A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale

I, the undersigned, have read this protocol and confirm that to the best of my knowledge, it accurately describes the planned conduct of the study.

SIGNATURE: **DATE:**

29/Nov/2018

Ilana Stancovski, PhD
Chief Scientific Officer
Mayne Pharma LLC

29-Nov-2018 | 11:06:54 EST

DocuSigned by:
Phoevos Hughes
Signer Name: Phoevos Hughes
Signing Reason: I approve this document
Signing Time: 29-Nov-2018 | 11:06 EST
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Phoevos Hughes, JD
Associate Director, Clinical Operations
Mayne Pharma LLC

DocuSigned by:
Joyce Rico
Signer Name: Joyce Rico
Signing Reason: I approve this document
Signing Time: 29-Nov-2018 | 15:33 EST
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29-Nov-2018 | 11:06:54 EST

Joyce Rico, MD, FAAD
Consultant Medical Expert
Premier Research

DocuSigned by:
Adrienne Kuxhausen
Signer Name: Adrienne Kuxhausen
Signing Reason: I approve this document
Signing Time: 29-Nov-2018 | 09:39 EST
6E6B87C6B98740819F26B8D5A7D662CF

29-Nov-2018 | 11:06:54 EST

Adrienne Kuxhausen, MS
Senior Biostatistician
Premier Research

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	Trifarotene (CD5789) Cream HE1
PROTOCOL NUMBER	18-ICH-001
EUDRACT NUMBER	2018-003272-12
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, and Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale
INDICATION	Lamellar ichthyosis
OBJECTIVES	Primary: To compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in adults and adolescents with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 12 weeks of treatment. Secondary: • To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% body surface area (BSA) twice weekly. • To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.
STUDY DESIGN	This is a 2-cohort, multicenter study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Visual Index for Ichthyosis Severity (VIIS) for scaling where 0 = clear and 4 = severe) on at least 2 areas of the 4 body areas assessed (chest/abdomen, back, arms, and legs). Adults (Cohort A) and adults and adolescents (Cohort B) will be randomized in a double-blind fashion to 1 of 2 doses of trifarotene cream HE1 or vehicle and treated twice weekly for 12 weeks. Subjects who complete the randomized, Double-blind Period of the study will be eligible to enter a 12-week, Open-label Extension (OLE) Period in which additional PK, safety, and efficacy data will be collected. Approximately 15 adults (≥18 years old) will be randomized into the first cohort of subjects (Cohort A) in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks. After the initial 15 subjects complete at least 28 days of treatment, an independent Data Safety Monitoring Board (DSMB) will review aggregate safety and tolerability data. If no safety issues are identified, both adults and adolescents (ages 12 to 17 years, inclusive) will be allowed to enroll in Cohort B. Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly for up to 12 weeks in the same manner as subjects in Cohort A. All subjects who complete the 12-week Double-blind Treatment Period will be eligible to enroll in the 12-week OLE Period. Subjects in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for up to 12 weeks.

After Screening, eligible subjects for Cohort A and B will enter a washout period of up to 35 days, during which they must stop using the following prohibited medications:

a. Topical treatments

Medication	Washout Period
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g., tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g., tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	-

b. Systemic treatments

Medication	Washout Period
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines (except Vitamin D analogues taken at stable dose since at least 1 month)	8 weeks
QT prolonging drugs	5 half lives
Enzymatic inductors (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (not all inclusive: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives

Study drug will be packaged in 50-g tubes from which up to 36 g of investigational product (IP) may be dispensed per application, i.e., the maximum dose per application. Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied.

Thereafter, each subject will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of product in a tube. Subjects will record the date and time of study treatment administration in the subject diary.

Local tolerability may differ in subjects with LI compared to healthy subjects, as their skin is drier and may be more sensitive. Local tolerability will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45 in the Double-blind Period; at Day 97 and 134 in the OLE Period) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability (Scale: 0–3 [none, mild, moderate, severe] for stinging/burning, pruritus, erythema) on each body area (chest/abdomen, back, arms, and legs) and the following procedures will be followed:

	- If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on that area only once weekly, until the score is back to <2; - If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3. Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and adverse events (AEs). All subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]) and any AEs, including application site reactions and concomitant medications used. Subjects will also be advised on permitted emollient(s) use on nontreatment days during the study; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Photographs will be taken at Baseline, Day 30 and Day 90 at selected sites with photographic capability for subjects who sign a separate photographic informed consent form (ICF). Samples for pharmacokinetic (PK) analysis will be drawn from all subjects at Baseline and at each clinic visit. In addition, a PK substudy is to be conducted at a limited number of sites. Participation in the PK substudy will be optional and will include at least 30 subjects, 15 adults and 15 adolescents. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for these subjects at each of the other clinic visits. Subjects who complete the Double-blind Treatment Period will have the option to continue into the OLE to assess safety for an additional 12-weeks with trifarotene cream HE1 200 µg/g twice weekly, on up to 90% of BSA, sparing the scalp, inguinal, and axillary areas. During the OLE Period, subjects will return to the site at Weeks 14, 16, 20, 24, and 26 for safety, tolerability, and efficacy assessments. Blood samples will be drawn for clinical laboratory safety tests and PK at Weeks 16 and 24. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 97 and Day 134) to assess safety; an unscheduled clinic visit may be performed, if necessary.
PLANNED NUMBER OF SUBJECTS	Approximately 120 total subjects; 15 adult subjects in Cohort A and 105 adult and adolescent subjects in Cohort B.
STUDY ENTRY CRITERIA	Inclusion criteria: 1. For Cohort A: subject is ≥18 years old; for Cohort B: subject is ≥12 years old. 2. Subject has known diagnosis of LI. 3. Subject has moderate to severe (VIIS 3-4) LI on at least 2 of the 4 body areas assessed (chest/abdomen, back, arms, and legs). 4. Subject has signed an ICF at Screening before any investigational procedures. Subjects <18 years of age (or Age of Majority) must sign an assent form in conjunction with an ICF signed by the parent/legal representative. 5. Subject who is participating in photography has signed a photography ICF. 6. Subject who is participating in the optional PK substudy has signed a PK ICF. 7. Subject is not of childbearing potential, i.e., a female who has not yet begun menstruating or who is postmenopausal (absence of menstrual bleeding for 1 year

	before Baseline, without any other medical reason, hysterectomy or bilateral oophorectomy),
	OR
	• Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception:
	  • bilateral tubal ligation
	  • combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline
	  • hormonal intrauterine device (IUD) inserted at least 1 month before Baseline
	OR
	Agrees to abstain from sex during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study.
	AND
	Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application.
	Note: Subjects who are premenstrual at Screening but begin menses during the study should follow the pregnancy testing schedule for WOCBP and must abstain from sexual intercourse while in the study and for at least 1 month after the last study drug application.
	8. Women of child-bearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine).
	9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent/assent, as applicable.
	10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).
	
	Exclusion criteria:
	1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization including syndromic ichthyoses.
	2. Subject has a history of or current moderate or severe stinging/burning at Screening.
	3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments.
	4. Subject with a known lipid disorder unless well controlled by stable doses of lipid-lowering agents for at least 6 months.
	5. Subject was previously treated with trifarotene/CD5789, including the acne formulation, or participated in previous studies for ichthyosis.
	6. Subject has known skeletal disease, hypertriglyceridemia, hypercholesterolemia, liver disease, or other poorly controlled medical conditions.
	7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome), Crohn's disease, or any other significant concomitant disease other than LI that, in the investigator's opinion, may

	put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 8. Subject is being treated for major depression disorder. 9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening. 10. Subject with any of the following laboratory values at Screening: a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory b. Triglycerides >200 mg/dL c. Total cholesterol >250 mg/dL d. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women e. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L. 11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments. 12. Subject has a history of long QT syndrome or clinically significant electrocardiogram (ECG) abnormalities, including clinically significant conduction disorders or significant arrhythmias, QTcF interval >450 ms, PR interval is not between 120 and 220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed. 13. Subject has a known allergy or sensitivity to any of the components of the investigational products. 14. Subject has been exposed to excessive ultraviolet (UV) radiations on the treated zones within 1 month before Baseline visit or who is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.). 15. Subject is inherently sensitive to sunlight. 16. Subject is presumed to be abusing drugs or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms. 17. Subject is participating in another interventional clinical trial.
INVESTIGATIONAL PRODUCT	Name: Trifarotene (CD5789) cream HE1 Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 100 µg/g or 200 µg/g applied topically twice weekly on up to 90% BSA Open-label Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) of 200 µg/g applied topically twice weekly on up to 90% BSA
REFERENCE PRODUCT(S)	Name: Vehicle cream Double-blind Period dose, route, frequency: A fixed dose (up to 36 g per dose, determined at Visit 2) applied topically twice weekly on up to 90% BSA
TREATMENT REGIMENS	Topical application twice weekly to all affected skin except the scalp, axillae, and inguinal area.
COORDINATING/ PRINCIPAL INVESTIGATOR	Keith A. Choate, MD Department of Dermatology, Yale University School of Medicine New Haven, CT 06520, USA
PLANNED STUDY SITES	Approximately 40 sites across North America, Europe, Israel, and Australia

CRITERIA FOR EVALUATION	Primary efficacy endpoint: The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0-4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs). Secondary endpoints: • The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices: – Investigator's Global Assessment (0-4) for each body area – Palm/sole Assessment (Scale: 0–4) – Individual score for roughness (Scale: 0–4) overall • Quality of life per Dermatology Life Quality Index (DLQI) • The difference in proportion of subjects with presence of fissures (presence/absence, number of fissures, and pain associated with fissures on a 0-3 scale) between the active trifarotene cream HE1 and vehicle groups Exploratory endpoints: • The difference in mean ectropion (Ectropion Severity Score [ESS] of 0–8) scores between the active trifarotene cream HE1 and vehicle groups • Quality of life per EQ-5D-5L Safety endpoints: • Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead ECGs • Local tolerability (Scale: 0–3 [none, mild, moderate, severe], determined by the investigator) on each of the 4 body areas (chest/abdomen, back, legs, arms) Pharmacokinetic endpoints: Plasma concentrations of CD5789 and its major metabolites will be measured.
STATISTICAL METHODS	Analysis Populations: The following are planned for the Double-blind Period of the study: The Safety population will be the primary population for analyses of safety and tolerability and will comprise all subjects who are randomized to treatment and receive at least 1 application of study drug. The intent-to-treat (ITT) population will comprise all randomized subjects. The modified intent-to-treat (mITT) population comprises all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. This population will be used as the primary population for the analysis of efficacy for the Double-blind Period of the study. The per protocol (PP) population will be defined prior to database lock and will comprise subjects in the mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations. The PK population includes all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. The PK population will be used to summarize all PK endpoints.

	The following populations are planned for the OLE period of this study: The OLE Safety population: all subjects who complete the 12-week Double-blind Treatment Period and receive at least 1 application of study drug in the OLE Period. OLE ITT population: all subjects who complete the 12-week Double-blind Period and who sign the OLE informed consent. The OLE mITT population: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6. The OLE PP population: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study. Subject Characteristics and Disposition: Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and baseline characteristics for all enrolled subjects. Medical history, physical examination findings, and vital sign measurements for all randomized subjects will be presented in listings. Efficacy Analyses: The number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT in the Double-blind Period will be presented. Generalized estimating equations (GEE) for binary response will be used to model the odds of successful resolution of LI with treatment group as a predictor. Other covariates, such as baseline VIIS scores, baseline characteristics, and interactions may be included. Various correlation matrix structures will be explored to model the within subject correlation. Additionally, the difference in mean VIIS score at Week 12/EOT between the active trifarotene cream HE1 groups and vehicle group will be analyzed using a 2-sided, 2-sample Wilcoxon rank-sum test at the 5% significance level; 95% confidence intervals will be presented. The VIIS scores as well as secondary and exploratory efficacy endpoints will be analyzed by visit using descriptive statistics through Week 24. Change from Baseline through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from Baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and Baseline score value as a covariate. Frequencies of results and 95% confidence intervals will also be reported, and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test. For subjects who report having fissures, the number of fissures and pain related to fissures will also be presented on a scale of 0–3 (none, mild, moderate, severe). Clinical Pharmacology Analyses: Noncompartmental PK analysis will be performed for the PK subset of subjects, as data permit. Plasma concentrations of CD5789 and its major metabolites will be measured and will be listed by subject. Safety Analyses: Safety and tolerability will be assessed based on the incidence of reported TEAEs, and SAEs, including relationship to study drug and severity, as well as physical examination findings, vital sign measurements (supine systolic blood pressure [SBP] and diastolic blood pressure [DBP] and pulse), clinical laboratory results (hematology, including serum aminotransferases and serum lipids, coagulation, clinical chemistry, and urinalysis) and 12-lead ECGs. Descriptive statistics for observed values and change from Baseline will be calculated at each visit within each study period and by treatment group within cohort.

SAMPLE SIZE DETERMINATION	The first cohort of 15 adult subjects is a reasonable sample size to assess safety and tolerability before enrolling adolescents. Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80% power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) using a 2-sample t-test assuming a mean difference of at least 1.0 and a standard deviation of 1.4 or lower. This study is not powered to detect a difference between the 2 active arms.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study will be as follows: 1. Screening and Washout: Up to 35 days (≥2 weeks washout for topical keratolytics, including urea and salicylic acid, and any topical retinoid or retinol [Vitamin A derivative], and ≥4 weeks washout for oral Vitamin A). 2. Double-blind study drug application: Twice weekly for up to 12 weeks. 3. Optional Open-label Treatment: Twice weekly for up to 12 weeks. 4. Follow-up: 14 days after last study drug application. The maximum study duration for each subject is approximately 229 days (33 weeks). The maximum treatment duration for each subject is 24 weeks.

2.2. Schedule of Events

Table 2-1: Schedule of Events for Double-blind Period

	Screening (-35 days to -1 day)	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[a,b] ± 7 days (ET)
Visit	**1**	**2**		**3**	**4**		**5**	**6**
Week		**1**		**2**	**4**		**8**	**12**
Written informed consent/assent	X							X[a]
Assign screening number	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical history	X							
Physical examination[c]	X	X						X
VIIS[d] assessment	X	X		X	X		X	X
Assign randomization number		X						
IGA assessment	X	X		X	X		X	X
Palm/sole assessment	X	X		X	X		X	X
Roughness, fissuring assessment[e]	X	X		X	X		X	X
Ectropion score	X	X		X	X		X	X
Photographs[f]		X			X			X
Quality of life per Dermatology Life Quality Index (DLQI)		X		X	X		X	X
EQ-5D-5L Quality of Life Questionnaire		X		X	X		X	X
Vital signs (blood pressure and pulse)	X	X		X	X		X	X

	Screening (-35 days to -1 day)	Double-blind Treatment Period						
		Baseline (Day 1)	Telephone Visit (Day 7)	Day 14 ± 5 days	Day 30 ± 7 days	Telephone Visit (Day 45)	Day 60 ± 7 days	Day 90[a,b] ± 7 days (ET)
Visit	**1**	**2**		**3**	**4**		**5**	**6**
Week		**1**		**2**	**4**		**8**	**12**
Height, weight, and BMI		X						X
12-lead ECG[g]	X	X			X			X
Clinical laboratory tests (hematology, chemistry, urinalysis)[h]	X	X			X			X
Serology (hepatitis B surface antigen, hepatitis C)	X							
Pregnancy test for female subjects (serum at Screening; urine subsequently)[i]	X	X			X		X	X
Assign randomization number		X						
PK blood sample collection[j]		X		X	X		X	X
Initial study drug application by clinic staff and measurement[k]		X						
Application instructions, advice on emollient use		X	X	X	X	X		
Dispense study drug and diaries[l]		X		X	X		X	
Concomitant medications	X	X	X	X	X	X	X	X
Tolerability assessment		X		X	X		X	X
Adverse events (and review diaries)		X	X	X	X	X	X	X
Collect all used/unused study drug[m]				X	X		X	X
Provide information about OLE option					X	X	X	

Abbreviations: BMI = body mass index; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears, nose, throat; ICF = informed consent form; IGA = Investigator Global Assessment; OLE = open-label extension; PK = pharmacokinetic; WOCBP = women of

childbearing potential; VIIS = Visual Index for Ichthyosis Severity

a. Day 90 procedures should be conducted for subjects who terminate the study early. If a subject discontinues IP, but continues to attend clinic visits, Day 90 will occur as scheduled. Day 90/Week 12 will be the first visit of the OLE Period for subjects who choose to continue (subjects will have up to 7 days to decide to sign the ICF and begin the OLE). Subjects who decide to continue into the OLE will have the following additional procedures: 1) sign informed consent; 2) will be weighed; 3) will be instructed on study drug application; 4) will be given new diaries, and 5) will be provided with study drug.
b. A Follow-up telephone call will be made within 14 days after Day 90 to subjects who choose not to continue into the Open-label Extension.
c. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
d. VIIS: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe for each of 4 body areas: chest/abdomen, back, arms, and legs (possible overall score = 16).
e. Roughness (0-4 scale); fissuring assessment: present/absent/number/pain (0-3 scale).
f. Photography will be performed at sites with the capability among subjects who sign a photographic ICF.
g. ECG to be conducted at Screening, Baseline, Day 30, and Day 90 for all subjects.
h. Subjects must be fasting (i.e., at least 8 hours)
i. Note: Subjects who are premenstrual at Screening but begin menses during the course of the study should follow the pregnancy testing schedule for WOCBP correlating to the visit menses began.
j. Samples for PK will be drawn from all subjects at Baseline and at each clinic visit. At selected sites among subjects who consent to participate in the PK substudy, samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1. On Day 30, IP will be applied in the clinic for PK substudy subjects, and PK samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose. Trough levels will be drawn when the subjects are in the clinic for other study visits (i.e., Day 14, Day 60, and Day 90).
k. Study staff will apply initial dose of study drug in the clinic after Baseline measurements, and the amount of study drug used will be measured (i.e., 36-g tube will be measured before and after application to determine amount used) to determine fixed dose.
l. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug tubes before dispensing; subjects must record days/times of study drug application in the diaries and any areas of skin not treated, e.g., due to local reactions). Dispense enough additional study drug until next visit (except at Day 90, unless subject consents to continue into OLE).
m. Confirm study drug compliance by measuring tube weight and reviewing diary.

Table 2-2: Schedule of Events for Open-label Extension

	Open-label Treatment Period						**Follow-up**
	Telephone Visit (Day 97)[a]	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7**	**8**		**9**	**10**	**11**
Week		**14**	**16**		**20**	**24**	**26**
Informed consent[a]							
Physical examination[b]						X	X
ECG			X			X	
VIIS[d] assessment		X	X		X	X	X
IGA assessment		X	X		X	X	X
Palm/sole assessment		X	X		X	X	X
Roughness, fissuring assessment[d]		X	X		X	X	X
Ectropion score		X	X		X	X	X
Vital signs (blood pressure and pulse)		X	X		X	X	X
Clinical laboratory tests (hematology, chemistry, urinalysis)[e]			X			X	
Pregnancy test for female subjects (urine)[f]			X		X	X	X
PK blood sample collection[g]			X			X	
Application instructions, advice on emollient use[h]	X	X	X	X			
Dispense study drug and diaries[i]		X	X		X		
Concomitant medications	X	X	X	X	X	X	X
Tolerability assessment		X	X		X	X	
Adverse events (and review diaries)	X	X	X	X	X	X	X

	Open-label Treatment Period						**Follow-up**
	Telephone Visit (Day 97)[a]	**Day 104 ± 5 days**	**Day 120 ± 7 days**	**Telephone Visit (Day 134)**	**Day 150 ± 7 days**	**Day 180 ± 7 days/ET**	**Day 194 or 14 days after End of Open-label Treatment**
Visit		**7**	**8**		**9**	**10**	**11**
Week		**14**	**16**		**20**	**24**	**26**
Collect all used/unused study drug[j]		X	X		X	X	

Abbreviations: ECG = electrocardiogram; ET = early termination; HEENT = head, eyes, ears, nose, throat; IGA = Investigator Global Assessment; PK = pharmacokinetic; VIIS = Visual Index for Ichthyosis Severity; WOCBP = women of childbearing potential

a. Subjects will sign the OLE ICF at the Double-blind Day 90/Week 12 Visit or within 7 days thereafter. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing and PK from Day 90/Week 12 will be carried over for the OLE Period and will not be repeated.
b. Limited physical examination to include HEENT, cardiorespiratory, abdomen, range of motion.
c. VIIS: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe for each of 4 body areas: chest/abdomen, back, arms, and legs (possible total score = 16).
d. Roughness (0-4 scale); fissuring assessment: present/absent/number/pain (0-3 scale).
e. Subjects must be fasting (at least 8 hours)
f. Note: Subjects who are premenstrual at Screening but begin menses during the course of the study should follow the pregnancy testing schedule for WOCBP correlating to the visit menses began.
g. Samples for PK will be drawn from all subjects at Day 120 and Day 180.
h. Subjects must record days/times of study drug application in the diaries and any areas of skin not treated (e.g., due to local reactions).
i. All subjects in the open-label extension will receive trifarotene 200 µg/g. Study drug provided in 50-g tubes (maximum single application is 36 g). Measure study drug tubes before dispensing. Dispense enough additional study drug until the next visit (except at Day 180)
j. Confirm study drug compliance by measuring tube weight and reviewing diary.

3. TABLE OF CONTENTS

3.1. List of In-Text Tables

3.2. List of In-Text Figures

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ATC	anatomical therapeutic chemical
AUC	area-under-the-curve
BMI	body mass index
BSA	body surface area
CFR	code of federal regulations
CI	confidence interval
C_{max}	maximum concentration
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressure
DLQI	dermatology life quality index
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ESS	ectropion severity score
FDA	Food and Drug Administration
GCP	good clinical practice
GEE	generalized estimating equations
HR	heart rate
IB	investigator brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IND	investigational new drug
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat

ABBREVIATION	EXPLANATION
IUD	intrauterine device
IWRS	interactive web response system
LI	lamellar ichthyosis
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
MMRM	mixed model of repeated measures
NCA	noncompartmental analysis
OC	observed case
OLE	open-label extension
PG	propylene glycol
PK	Pharmacokinetic(s)
PoC	proof-of-concept
PP	per-protocol
QTc	QT interval corrected for heart rate
RARγ	retinoid acid receptor γ
RBC	red blood count
RR	respiratory rate
RXR	retinoid X receptor
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
TEAE	treatment-emergent adverse event
T_{max}	time of C_{max}
UAE	unexpected adverse event
UADR	unexpected adverse drug reaction
US	United States
UV	ultraviolet
VIIS	Visual Index for Ichthyosis Severity
WHO-DD	World Health Organization Drug Dictionary
WOCBP	women of child-bearing potential

5. INTRODUCTION

5.1. Background and Rationale

The ichthyoses comprise a large group of skin scaling disorders with diverse etiology. The stereotypic pathophysiology is epidermal hyperplasia and the formation of excess stratum corneum accompanied by abnormal (delayed and/or disordered) desquamation, with visible accumulation of squames (scales) on the skin's surface – the clinical hallmark of all the ichthyoses.

Lamellar ichthyosis (LI) is recognized as a severe form of ichthyosis that persists throughout life. During the first postnatal weeks, the hyperkeratotic membrane patients are typically born with is gradually shed, and is replaced by scaling and lichenification that involves the entire body including the intertriginous areas, palms, soles, and scalp. While usually not life threatening, LI can result in disability, partial deafness, poor adaptation to environmental conditions (due to hypohydrosis), severe discomfort (pruritus, fissuring of the skin) and significant psychosocial impact.

Lamellar ichthyosis, a member of the nonsyndromic autosomal recessive congenital ichthyosis group of ichthyoses, has an incidence of 1 per 100,000–300,000 live births.[1] Lamellar ichthyosis is undoubtedly a rare disease.

Therapeutic approaches for LI are mainly based on the use of topical emollients, keratolytic agents (urea, lactic acid, salicylic acid), topical retinoids and, in severe cases, oral retinoids.[3,3]

Oral retinoid usage in LI is mainly based on case reports and case series.[4,5,6,7,8] The mechanism of retinoid action involves modulation of keratinocyte differentiation, keratinocyte hyperproliferation and tissue infiltration by inflammatory cells. Systemic retinoids (such as acitretin, etretinate, or isotretinoin) have been found to be efficacious in the treatment of severe ichthyoses, especially in LI.[6]

Vahlquist, et al (2008)[3] report that by combining 2 or more keratolytic agents and moisturizers in the same lipophilic cream base, it is often possible to achieve additive or even synergistic effects in LI without the need to use irritating concentrations of either agent alone. In a double-blind trial of 4 different cream mixtures in 20 patients with LI, a mixture of 5% lactic acid and 20% propylene glycol (PG) in a semi-occlusive cream for 4 weeks twice daily was significantly more effective than 20% PG or 5% urea alone in the same vehicle.[9] Although the treatments were well tolerated, an efficient removal of hyperkeratosis without correcting the underlying biochemical defect in LI is likely to deteriorate the patient's intrinsic barrier problem, because an excessive production of corneocytes probably represents a homeostatic response to an ineffective barrier. Indeed, transepidermal water loss increased after successful treatment of LI with either topical keratolytics[9] or oral retinoid.[10] Although this may not be noticeable by the patient, even minor deteriorations in the barrier function can enhance transcutaneous penetration of active cream ingredients or other topically applied chemicals, which is a matter of special concern in children. Accordingly, α-hydroxy acids and salicylic acid should not be used at all in babies and only with great caution when treating large, eroded skin areas in adult patients.[11,12]

Many patients with LI use pumice, foot files, or gentle rubbing of the skin after a hot bath or a shower to remove scales and hyperkeratosis. Overnight occlusion of problematic skin areas with plastic sheets after applying a thick layer of emollient or keratolytic agents is another way of potentiating therapy, especially on the scalp, which is notoriously difficult to treat. Although

usually effective, all these remedies may further damage the skin barrier and lead to exaggerated epidermal proliferation, erythema, painful erosions and increased trancutaneous penetration.[3]

Based on this information, LI has significant unmet medical need for safer and more effective therapies.

5.1.1 CD5789 (Trifarotene)

CD5789 is a new chemical entity discovered by Galderma R&D SNC and formulated for topical application. It is a novel retinoid acid receptor γ (RARγ) agonist, characterized by its high specificity to this receptor. CD5789 is selective for RARγ over RARα and RARβ (approximately 50- and 8-fold, respectively), with no retinoid X receptor (RXR) activity. CD5789 is currently under clinical development for the topical treatment of various dermatoses, including acne vulgaris and LI.

The pharmacological retinoid-like properties of CD5789 were confirmed in in vitro and in vivo models, showing its interest for its development in the treatment of LI. Therefore, it may have an effect on the differentiation and hyperproliferation of keratinocytes, and consequently improve hyperkeratotic skin of patients with lamellar ichthyosis.

Within the overall acne development program at Galderma, CD5789 has been tested in different pharmaceutical forms for topical administration. As of 15-Jan-2018, 6 different formulations have been evaluated: a solution, a gel and 4 creams (CD5789 cream A, CD5789 cream B, CD5789 cream HE1 concept and its optimized version, cream HE1), with different concentrations (up to 400 µg/g). Therefore, several formulations at different CD5789 concentrations have been tested in nonclinical and clinical development programs.

Galderma decided to develop a new cream formulation that might better address the issue of skin dryness in patients with LI. This formulation was named “Cream HE1 concept.” It has been preliminarily investigated in an exploratory trial in psoriasis at concentrations up to 400 µg/g (RD.03.SRE.40204E). In a proof-of-concept study (RD.03.SRE.40181E), positive results were also obtained in patients with LI with CD5789 cream (up to 100 µg/g) that was effective in decreasing scaling and roughness. Based on these results, a new CD5789 formulation (cream HE1) was developed for further clinical investigations in LI. The formulation cream HE1 was developed with the objective to obtain a formulation with appropriate stability of the active ingredient and in which CD5789 would be homogeneously dissolved in the oily phase at a higher concentration compared to the cream formulation used in the acne program. Cream HE1 contains 100, 200, or 400 µg/g (0.01% [w/w], 0.02% [w/w], 0.04% [w/w], respectively) of CD5789.

Galderma has granted Mayne Pharma LLC an exclusive license to develop and commercialize CD5789 (trifarotene) for LI and other orphan diseases; therefore, the LI indication is no longer pursued by Galderma.

5.2. Clinical Experience

The cream HE1 differs from the CD5789 cream used to treat acne vulgaris in that it contains fewer excipients with drying effects and therefore may be better suited for patients with LI.

Throughout the 30 clinical studies that comprise the clinical development program for CD5789 topical products, 1976 subjects were exposed to CD5789. No systemic safety concerns related to CD5789 gel or creams, or cream HE1 at doses up to 400 µg/g were reported. The subjects were

exposed to a maximal total CD5789 dose of 36 g/day (Investigator's Brochure for CD5789 Cutaneous Formulation).

The CD5789 PK profile was also investigated using cream HE1 (Study GD.03.SRE.103813) in 36 healthy volunteers of Japanese and non-Japanese origin. Subjects were treated daily on up to 90% of body surface area (BSA) for 29 days with up to 36 g of cream formulation. Both CD5789 100 μg/g and 200 μg/g cream HE1 were investigated. Plasma PK assessment demonstrated that repeated topical applications of CD5789 cream HE1 resulted in low and similar CD5789 systemic levels in all treatment groups. In addition, no systemic safety concerns were raised from this healthy volunteer study in which cream HE1 200 μg/g was applied daily under maximal-use conditions on almost the full body. In this study, however, the level of irritation resulted in the need to decrease the frequency of application to twice weekly (Investigator's Brochure for CD5789 Cutaneous Formulation).

5.3. Summary of Potential Risks and Benefits

Although the primary objective of this study is safety in the patient population with LI, the potential benefits of study participation are that subjects with LI may experience a reduction in their LI symptoms as a result of treatment with trifarotene (CD5789) cream HE1. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to trifarotene (CD5789) cream HE1 and the risks of medical evaluation, including venipuncture.

Animal studies with CD5789 have shown reproductive toxicity in the embryo-fetal studies. Despite low systemic levels with the CD5789 concentration of 50 μg/g used in patients with acne, CD5789 must not be administered during pregnancy.

When CD5789 is used in the other formulations and/or for other indications and/or with higher concentrations or higher application surface areas, the potential risk of teratogenicity needs to be considered as the safety margin may be lower. Depending on the study population and conditions mentioned above, or other specific requirements, the appropriate contraception method is described in this protocol.

It is unknown whether CD5789 or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Lactating women are not eligible for the clinical study.

Certain cutaneous signs and symptoms of irritation and localized reactions at the application site such as erythema, scaling, dryness, stinging/burning, and pruritus may be experienced with use of CD5789. Depending upon the severity of these side effects, subjects may be instructed to reduce the frequency of application or to discontinue use.

Trifarotene cream contains propylene glycol that is mildly irritant to the skin, eyes, and mucous membranes. Trifarotene (CD5789) cream HE1 also contains butylated hydroxytoluene that may cause local skin reactions (e.g., contact dermatitis), or irritation to the eyes and mucous membranes and sodium benzoate that is mildly irritant to the skin, eyes, and mucous membranes.

CD 5789 is mildly irritant to the skin, eyes, and mucous membranes. Therefore, it should not come into contact with the eyes, mouth, or mucous membranes.

There is a potential risk of skin sensitization. If a reaction suggesting sensitivity to trifarotene (CD5789) cream HE1 occurs, the use of the trifarotene cream HE1 must be discontinued.

There is a potential risk of photosensitivity disorder (sunburn). Excessive exposure to sunlight or ultraviolet (UV) radiation (i.e., occupational exposure to the sun, planned holidays in the sun during the study, phototherapy, tanning salon) must be avoided during the studies.

As reported with other topical retinoids, there is a potential risk of pigmentation disorders.

A summary of the pharmaceutical properties and known potential risks of trifarotene (CD5789) cream HE1 is provided in the current version of the investigator brochure (IB). The investigator must become familiar with all sections of the trifarotene (CD5789) cream IB before the start of the study.

6. OBJECTIVES

6.1. Primary Objective

The primary objective is to compare the safety and efficacy of 2 concentrations of trifarotene cream HE1 versus vehicle in adults and adolescents with moderate to severe autosomal recessive ichthyosis with lamellar scale, also known as lamellar ichthyosis (LI) after 12 weeks of treatment.

6.2. Secondary Objectives

The secondary objectives are as follows:

- To assess systemic exposure to trifarotene and its major metabolites after topical application of the investigational product (IP) on up to 90% BSA twice weekly.
- To assess safety for up to 24 weeks of dosing with open-label trifarotene cream HE1 200 µg/g.

7. STUDY DESIGN

7.1. Overall Study Design and Plan

The first part of this study is a phase 2, randomized, 2-cohort, double-blind, vehicle-controlled, multicenter study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in adults and adolescents with LI. Adult and adolescent subjects who complete the randomized, double-blind, vehicle-controlled period of the study will be eligible to continue into an open-label extension (OLE) period and be treated with trifarotene cream HE1 200 µg/g for an additional 12 weeks.

The randomized, double-blind, vehicle-controlled period of the study in subjects with moderate to severe LI (i.e., 3–4 on a 5-point Visual Index for Ichthyosis Severity [VIIS] index for scaling where 0 = clear and 4 = severe on at least 2 of 4 areas of the body: chest/abdomen, back, arms, and legs), is designed to compare the safety of 2 doses of trifarotene cream HE1 with that of vehicle in the treatment of LI.

After Screening, eligible subjects for Cohorts A and B will enter a washout period of up to 35 days, during which they must stop using prohibited topical and systemic treatments with designated washout periods (Table 9-1).

The first cohort of subjects (Cohort A) will randomize approximately 15 adults (≥18 years old) in a 1:1:1 ratio to trifarotene (CD5789) cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle.

Study drug will be packaged in 50-g tubes from which up to 36 g of IP may be dispensed per application, i.e., the maximum dose per application. Study staff will apply the first dose of study drug to each subject in the clinic on Day 1 after Baseline measurements, and will record the amount of study drug applied (i.e., study staff will measure the 50-g tube before and after the first application to determine the fixed dose amount for each subject). Thereafter, subjects will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than the full amount of IP in a tube.

Subjects enrolled in Cohort A will continue treatment for up to 12 weeks.

After the initial 15 subjects complete at least 28 days of treatment, an independent Data Safety Monitoring Board (DSMB) will review aggregate safety and tolerability data. If no safety issues are identified, both adults and adolescents (ages 12–17 years, inclusive) will be allowed to enroll in Cohort B (up to approximately 105 subjects). Subjects in Cohort B will be randomized 1:1:1 to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and similarly treated twice weekly for up to 12 weeks in the same manner as subjects in Cohort A.

Subjects will be provided with diaries in which to record study drug application (days/times and any areas of skin not treated [e.g., due to local reactions]), any application site reactions, adverse events (AEs), and concomitant medications used. Subjects will also be advised on permitted emollient(s) use on nontreatment days during the study; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited.

Photographs will be taken at Baseline, Day 30, and Day 90 in the Double-blind Period at selected sites with photographic capability for subjects who signed a separate photographic informed consent form (ICF).

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit, as indicated in the Schedule of Events (Table 2-1).

In addition, a PK substudy will be conducted at specific sites with the capability to conduct it. Participation in the PK substudy will be optional and will include at least 15 adults and 15 adolescents. Subjects who participate in the PK substudy will come from both study cohorts and will undergo serial blood sampling predose and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30. Trough levels will be drawn for all subjects at specified time points.

Efficacy will be assessed by the number of subjects in each treatment group who achieve "success" defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/end-of-treatment (EOT) in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0-4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs). In addition, efficacy criteria include assessment of the Investigator Global Assessment (IGA; scale: 0-4 for each body area: chest/abdomen, back, legs, and arms), scales for palm/sole, roughness, fissuring, and the Dermatology Life Quality Index (DLQI), and the EQ-5D-5L Quality of Life (QoL) Questionnaire. Ectropion Severity Scores (ESS) between the active trifarotene cream HE1 and vehicle groups will be an exploratory endpoint.

Plasma concentrations of CD5789 and its major metabolites will be measured.

Safety will be assessed by evaluating reported adverse events (AEs), changes in clinical laboratory test results, vital sign measurements, physical examinations, 12-lead electrocardiograms (ECGs), and local tolerability.

All AEs observed by the study personnel or reported by the subject during the study (from the time of the signing of the informed consent and/or assent through the posttreatment visit) will be documented.

Topical trifarotene cream HE1 was generally well tolerated in recently completed phase 3 pivotal and long-term safety studies in subjects aged 9 years and older with acne vulgaris. The local tolerability of the trifarotene cream HE1 formulation in subjects with LI is unknown and will be monitored during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability (Scale: 0–3 [none, mild, moderate, severe]) on each body area (chest/abdomen, back, legs, arms) and will follow the procedures detailed in Section 9.4.

Subjects who complete the 12-week Double-blind Treatment Period will have an option to continue into an OLE Period for an additional 12 weeks with trifarotene cream HE1 200 µg/g. During the OLE Period, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and Week 24 from all subjects who continue into the OLE Period (Table 2-2).

Stopping rules and treatment modification will be defined at the subject level based on local tolerability, selected laboratory parameters, and AEs; see Section 9.4.

Figure 7-1: Double-blind Study Design

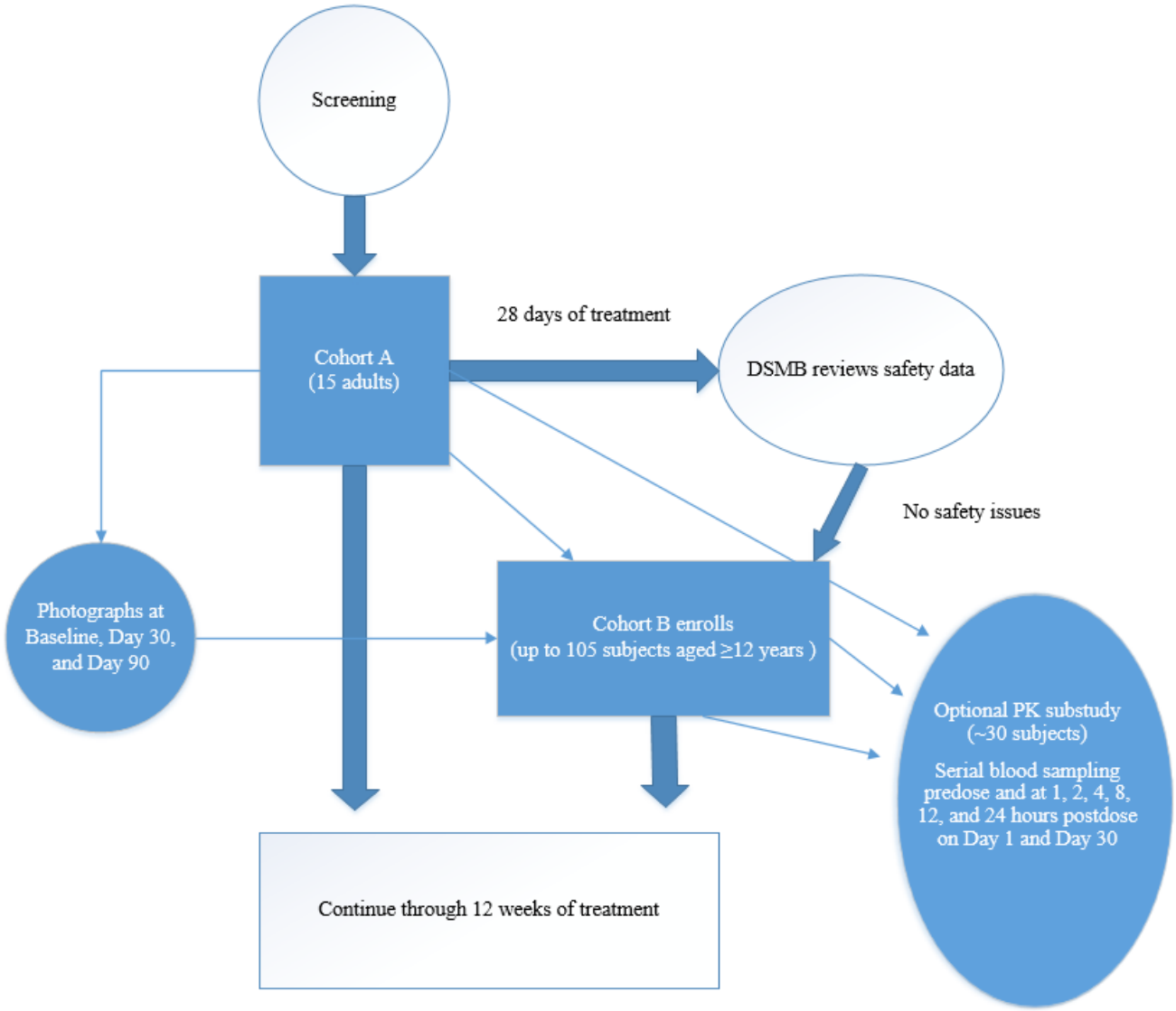
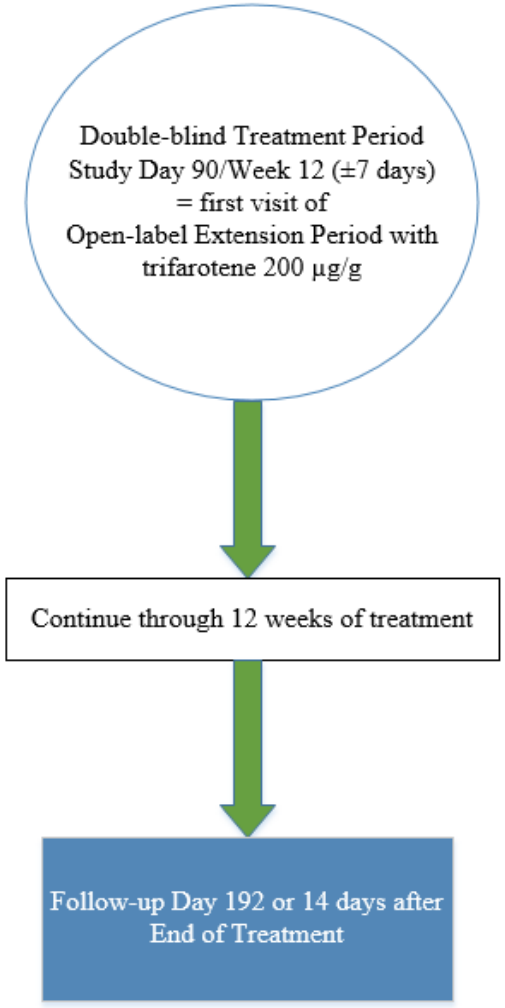


Figure 7-2: Open-label Study Design



7.2. Rationale and Discussion of Study Design

The first part of this study is a randomized, double-blind, placebo-controlled study of the safety, tolerability, PK, and efficacy study of trifarotene cream HE1 100 µg/g and 200 µg/g in adults and adolescents with LI.

In a previous proof-of-concept study (RD.03.SRE.40181E), subjects with LI applied trifarotene 50 and 100 µg/g cream to limited areas and results demonstrated a decrease in scaling with good safety and tolerance. In a phase 1 study in healthy Japanese and non-Japanese subjects (RD.03.SPR.103813), repeated topical applications of trifarotene (CD5789 cream HE1) 100 µg/g and 200 µg/g resulted in low and similar CD5789 systemic levels in all the cohorts. These studies are fully described in the current Investigational Brochure.

To ensure safety, this phase 2 study will begin with an initial cohort (Cohort A) of 15 adults randomized 1:1:1 to trifarotene cream HE1 100 µg/g, 200 µg/g, or vehicle to be applied twice weekly. An independent DSMB will review aggregate safety and tolerability data from the initial 15 subjects' first 28 days of treatment. If no safety issues are identified, 105 adults and adolescents (ages 12–17 years, inclusive) will be allowed to enroll in Cohort B and randomized to trifarotene cream HE1 100 µg/g, trifarotene cream HE1 200 µg/g, or vehicle and treated twice weekly in the same manner as subjects in Cohort A. All subjects in the randomized, double-blind portion of the study will be treated for up to 12 weeks and data on safety, tolerability, PK, and efficacy collected.

Adult and adolescent subjects who successfully complete the initial 12 weeks of double-blind treatment will have the option to enter an OLE with trifarotene cream HE1 200 ug/g twice weekly for up to 12 weeks.

The OLE will collect additional safety, tolerability, PK, and efficacy data. As designed, this study will provide important information on safety, tolerability, and PK with dosing of adolescents and adults with LI for up to 6 months.

The protocol includes appropriate monitoring for safety and tolerability. If subjects develop significant local application site reactions or tolerability issues, the protocol includes language for reducing the frequency of application or halting study drug application until the symptoms abate.

7.3. Selection of Doses in the Study

Based on the results from Study RD.03.SRE.40181E and Study SRE.103813, the doses of 100 µg/g and 200 µg/g were selected for further investigation in adult and adolescent subjects with moderate to severe LI. The PoC study demonstrated efficacious treatment with 100 µg/g in adults. The PK and tolerability study showed that, when the frequency of application was reduced from daily to twice weekly, the 200 µg/g cream HE1 had good local tolerability.

Therefore, the current study will use these doses compared with vehicle, applied twice weekly on up to approximately 90% BSA in subjects with LI.

7.4. Study Sites

The study will take place at approximately 40 sites in North America, Europe, Israel, and Australia.

7.5. Point of Contact

A point of contact will be identified to provide information to subjects about where to obtain information on the study, the rights of subjects, and whom to contact in case of a study-related

injury. This information will be provided in the subject information and informed consent form (ICF).

7.6. End of Study Definition

A clinical trial is considered completed when the last participant's last study visit has occurred.

8. SUBJECT POPULATION

8.1. Selection of Study Population and Diagnosis

Diagnosis of LI for the purposes of this study will be a clinical diagnosis. Although some younger subjects may have had genetic testing, older subjects may not.

While LI is a rare disease and subject enrollment may be challenging, due to possible bias introduced by including household members in the same study, it is recommended that only 1 household member be included in the study to maintain the blind and ensure all assessments are independent.

8.2. Study Entry Criteria

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. For Cohort A: subject is ≥18 years old; for Cohort B: subject is ≥12 years old.
2. Subject has known diagnosis of LI.
3. Subject has moderate to severe (VIIS 3–4) LI on the at least 2 of the 4 body areas assessed (chest/abdomen, back, arms, and legs).
4. Subject has signed an ICF at Screening before any investigational procedures. Subjects <18 years of age (or Age of Majority) must sign an assent form in conjunction with an ICF signed by the parent/legal representative.
5. Subject who is participating in optional photography has signed a photography ICF.
6. Subject who is participating in the optional PK substudy has signed a PK ICF.
7. Subject is not of childbearing potential, i.e., a female who has not yet begun menstruating or who is postmenopausal (absence of menstrual bleeding for 1 year before Baseline, without any other medical reason, hysterectomy or bilateral oophorectomy),

   OR

- Subject is a woman of childbearing potential (WOCBP) or a male subject with sexual partners capable of reproduction who agrees to use 2 effective forms of contraception during the study and for at least 1 month after the last study drug application. The 2 authorized forms of contraception are condom used with 1 of the following methods of contraception:
  - bilateral tubal ligation
  - combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month before Baseline
  - hormonal intrauterine device (IUD) inserted at least 1 month before Baseline

  OR

  Agrees to abstain from sex during study participation and for 1 month after the last application of study drug and to use a highly effective contraceptive as backup if he or she becomes sexually active during the study.

  AND

Male subjects may not donate sperm during the study and for at least 1 month after the last study drug application.

Note: Subjects who are premenstrual at Screening but begin menses during the study should follow the pregnancy testing schedule for WOCBP and must abstain from sexual intercourse while in the study and for at least 1 month after the last study drug application.

8. Women of child-bearing potential must be nonlactating and have negative pregnancy test results at Screening (serum) and on Day 1 before study drug administration (urine).
9. Subject is reliable and capable of adhering to the protocol and visit schedule, in the investigator's judgment, and has signed informed consent/assent, as applicable.
10. Subject is taking no more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

8.2.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets any of the following criteria:

1. Subject has any variant of ichthyosis other than LI or another disorder of keratinization including syndromic ichthyoses.
2. Subject has a history of or current moderate or severe stinging/burning at Screening.
3. Subject has an ongoing cutaneous infection or any other significant concomitant skin disease (other than the LI) which, in the investigator's opinion, may interfere with the study assessments.
4. Subject with a known lipid disorder unless well controlled by stable doses of lipid-lowering agents for at least 6 months.
5. Subject was previously treated with trifarotene/CD5789, including the acne formulation, or participated in previous studies for ichthyosis.
6. Subject has known skeletal disease, hypertriglyceridemia, hypercholesterolemia, liver disease, or other poorly controlled medical conditions.
7. Subject has a medical condition that potentially alters bone metabolism (e.g., osteoporosis, thyroid dysfunction, Cushing syndrome), Crohn's disease, or any other significant concomitant disease other than LI that, in the investigator's opinion, may put him or her at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
8. Subject is being treated for major depression disorder.
9. Subject with positive serology for hepatitis B surface antigen, hepatitis C, or are known to be HIV positive or to have AIDS at Screening.
10. Subject with any of the following laboratory values at Screening:
    a. Aspartate aminotransferase or alanine aminotransferase >1.5 × upper limit of normal defined by the laboratory
    b. Triglycerides >200 mg/dL
    c. Total cholesterol >250 mg/dL
    d. Hemoglobin <12.5 g/dL for men and <11.5 g/dL for women
    e. Platelets $<150 \times 10^9$/L or $>400 \times 10^9$/L.

11. Subject has any clinically other significant abnormal laboratory value (hematology, chemistry, or urinalysis) at Screening that, in the investigator's opinion, may put the subject at risk if he or she takes part in the study, and/or that may interfere with the study assessments.
12. Subject has a history of long QT syndrome or clinically significant ECG abnormalities, including clinically significant conduction disorders or significant arrhythmias, QTcF interval >450 ms, PR interval is not between 120 and 220 ms (inclusive), HR >100 bpm or <50 bpm, QRS interval >110 ms, or QT intervals that cannot be consistently analyzed.
13. Subject has a known allergy or sensitivity to any of the components of the investigational products.
14. Subject has been exposed to excessive UV radiations on the treated zones within 1 month before Baseline visit or who is planning intensive UV exposure during the study (e.g., occupational exposure to the sun, sunbathing, phototherapy, etc.).
15. Subject is inherently sensitive to sunlight.
16. Subject is presumed to be abusing drug or alcohol at Screening or Baseline Visits based on medical history or current clinical symptoms.
17. Subject is participating in another interventional clinical trial.

8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

8.4. Discontinuation of Study Intervention

Discontinuation from study treatment does not mean withdrawal from the study, and the remaining study procedures should be completed as indicated in the study protocol (see Section 10.2.4.5). If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

An investigator may discontinue a participant's study treatment for any of the following reasons:

- Pregnancy
- Significant study intervention noncompliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for discontinuation of study treatment will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, are randomized, and receive the study intervention, and subsequently discontinue study treatment, or are withdrawn from the study will not be replaced.

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.5. Subject Replacement Criteria

Withdrawn subjects will not be replaced. If a substantial number of subjects are withdrawn from the study, the sponsor will evaluate the need for developing replacement criteria.

Randomized subjects withdrawn from the study may not reenter. The subject number for a withdrawn subject will not be reassigned to another subject.

9. TREATMENTS

9.1. Identification of Investigational Product(s)

Trifarotene cream HE1 is a cream containing 100 or 200 µg/g (0.01% [w/w] or 0.02% [w/w], respectively) of CD5789 and the following excipients: purified water, propylene glycol, allantoin, glycerin, medium-chain triglycerides, polypropylene glycol 15 stearyl ether, cyclomethicone, phenoxyethanol, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane (simulgel 600 PHA), sodium benzoate, butylated hydroxytoluene, and gluconolactone.

Vehicle contains the same ingredients, without the CD5789.

Trifarotene cream HE1 and vehicle will be provided in cream form for topical application and will be supplied in 50-g tubes from which a maximum of 36 g of IP may be extracted,

Trifarotene cream HE1 and vehicle will be supplied by G. Production, Inc. (Galderma) in Baie-D'Urfé, QC, Canada.

9.2. Treatments Administered

For the Double-blind Treatment Period, a fixed dose (determined at Visit 2) of trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream will be applied topically twice weekly on up to 90% BSA of each subject.

Study staff will apply the first administration of IP in the clinic on Day 1 after Baseline measurements, and the amount of IP used will be measured (i.e., 50-g tube will be measured before and after application to determine amount used).

The maximum dose per application is 36 g (i.e., 1 tube). Subjects will receive an adequate number of tubes to use 1 tube per application and will use a new tube for each treatment day. Subjects may use less than full amount of product in a tube.

After the Day 1 visit, subjects will apply approximately the same amount (up to 36 g) of study drug as for the first dose on up to 90% of BSA twice weekly, sparing the scalp, inguinal, and axillary areas. Subjects will continue treatment for up to 12 weeks.

For the OLE Period, all subjects will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the Double-blind Period for an additional 12 weeks.

Subjects should not apply IP on visit days until after the visit.

9.3. Selection of Timing of Dose for Each Subject

Subjects will be randomized in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. After Day 1, on which the study staff will apply the first administration of IP in the clinic, each subject will apply approximately the same amount of IP on up to 90% of their BSA twice weekly. It is suggested that each subject choose 2 specific days per week at least 3 days apart on which to apply their IP (e.g., Tuesday and Friday), and maintain that regimen throughout the study.

All subjects will be provided with diaries in which to record study drug application (days/times) and any areas of skin not treated (e.g., due to local reactions).

If a subject misses an IP application, they should apply the IP as soon as they remember and record the date/time in the subject diary, then wait at least 3 days and continue their regimen.

Subjects should not shower, bathe, or swim for at least 4 hours after IP application. No occlusive dressings should be used on areas to which IP is applied.

Subjects who continue into the Open-label Extension will receive trifarotene cream HE1 200 µg/g and apply the same fixed dose in the same manner as in the double-blind period for an additional 12 weeks.

9.4. Dose Adjustment Criteria

Local tolerance will be followed very carefully during the study. Subjects will receive information on study drug use and stopping rules and will be instructed to contact the site with any safety/tolerability issues. Study personnel will telephone subjects in between scheduled visits (i.e., at Day 7 and Day 45) to assess safety; an unscheduled clinic visit may be performed, if necessary. During all clinic visits, the investigator will assess local tolerability on a 0–3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) on each of the 4 body areas (chest/abdomen, back, legs, arms), and the following procedures will be followed:

- If a score of 2 (moderate) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will be applied on this area only once weekly, until the score is back to <2;
- If a score of 3 (severe) is recorded on a local tolerability assessment scale (stinging/burning, pruritus, erythema) on any treated area, the study drug will not be applied on that area until the score is back to <3.

9.4.1 Stopping Rules

A subject's treatment in either the Double-blind Period or the Open-label Extension must be stopped if any of the following occur:

- Subject becomes pregnant or suspects they are pregnant
- Subject has severe (score of 3) local application site AEs that do not abate with 'drug holiday' and reintroduction of IP.
- Subject has clinically significant changes in laboratory values (liver function tests, cholesterol/triglycerides – which may occur with systemic retinoid use)

9.5. Treatment Compliance

Subjects will be asked to record their twice-weekly applications of IP in the diary during both the Double-blind and OLE Periods. Deviations from the planned doses (missed dose or timing) will be recorded on the subject's eCRF. Study personnel will review diaries at each visit and diaries will be collected as source documents. Information from subject diaries will be transcribed on the appropriate eCRF pages for documentation of subject compliance with the IP.

Study personnel will assess treatment compliance with IP regimens by weighing IP tubes before dispensing and upon return and by questioning the subject, at every post-randomization visit. A participant is compliant with study product if he or she takes at least 80% of the scheduled doses as assessed by diary entries, supplemented by tube weight. A subject who is not compliant (used

80–120% of IP tubes) will be counseled at each visit on the importance of using the IP as instructed.

9.6. Method of Assigning Subjects to Treatment Groups

In the double-blind, parallel-group, randomized period of the study, subjects who meet study entry criteria will be randomly assigned in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects are entered into the study. Study center will not be a blocking factor in the randomization schedule.

Premier Research will prepare the randomization schedule before the start of the study. No one involved in the study performance will have access to the randomization schedule before the official unblinding of treatment assignments. No subject will be randomized into this study more than once.

In the OLE Period, all subjects will receive trifarotene cream HE1 200 µg/g.

9.7. Blinding and Unblinding Treatment Assignment

All subjects, investigators, and study personnel involved in the conduct of the Double-blind Period of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician and programmer from Premier Research who will have access to the randomization code. The statistician will have access to unblinded data if there is an unblinded DSMB review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will use the IWRS code. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

The primary analysis period is the first 12 weeks of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after database lock has been achieved. A second analysis will take place for endpoints assessed from Week 12 through the OLE Period.

9.8. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

All subjects must washout the following medications after enrollment and before randomization:

Table 9-1: Washout Periods for Prohibited Medications

Medication	Washout Period
Topical Treatments	
Corticosteroids (except inhaled and ophthalmic corticoids)	2 weeks
Retinoids (e.g. tretinoin, tazarotene)	4 weeks
Vitamin D analogues	2 weeks
Immunosuppressants (e.g. tacrolimus)	2 weeks
Antracen derivatives, tar and salicylic preparations	2 weeks
Keratolytics (such as urea, lactic acid, propylene glycol, salicylic acid) except keratolytic shampoo	-
Systemic treatments	
Retinoids	8 weeks
Oral Vitamin A supplementation more than 3500 IU per day	2 weeks
Medication interfering with bone activity, e.g., corticosteroids, thyroid hormones, cytotoxics, bisphosphonates, calcitonins, tetracyclines, quinolones, thiazides, salicylates in long-term course, heparin, theophylline, barbiturates, colchicines (except Vitamin D analogues taken at stable dose since at least 1 month)	8 weeks
QT prolonging drugs	5 half lives
Enzymatic inductors (such as rifampicine, phenytoin, carbamazepine, phenobarbital, St. John's Wort)	3 months
CYP2C9 and 2C8 inhibitors (not all inclusive: gemfibrozil, fluconazole, fluvoxamine, sulfaphenazole, miconazole, amiodarone, sertraline, sulfamethoxazole, valproic acid, voriconazole, trimethoprim, rosiglitazone, pioglitazone)	5 half lives

9.8.1 Permitted Therapies

Subjects will be advised on permitted emollient(s) for use on nontreatment days during the study; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited.

Other concomitant medications are allowed (e.g., analgesics, antihistamines), but should be limited to those medications considered necessary. All concomitant medications, both prescribed and over-the-counter, should be recorded in the eCRF.

9.8.2 Prohibited Therapies

The therapies listed in Table 9-1 are prohibited during the study.

Subjects may not use concomitant keratolytics such as urea, salicylic acid, alpha, or beta hydroxyacids. Subjects may not use topical or systemic retinoids. Subjects may not take more than 3500 IU/day Vitamin A (e.g., as in a multivitamin).

Subjects receiving excluded therapies will be ineligible for study enrollment or for continued treatment in the study, at the investigator's discretion with consultation with Mayne Pharma LLC and the medical monitor.

9.8.3 Restrictions

Subjects should not shower, bathe, or swim within 4 hours of study drug application. No occlusive dressings should be applied to areas where study drug was applied.

Subjects should only use investigator-approved emollients, and should not use them on treatment days within 4 hours of study drug application.

9.9. Treatment After End of Study

After the end of the study, each subject will be treated according to standard clinical practice.

9.10. Dispensing and Storage

The test product supplied by Mayne Pharma LLC is to be used exclusively in the clinical study according to the instructions of this protocol. The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Premier Research. Until the IP is dispensed to the subjects, it must be stored at 20–25°C (68–77°F), with excursions permitted to 15–30°C (59–86°F); do not freeze and with the tube kept tightly closed in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

9.11. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of subjects (subject number) who received the IP. The investigator will not supply the IP to any person except those named as subinvestigators on the Form Food and Drug Administration (FDA) 1572, designated study personnel, and subjects in this study. The investigator will not dispense the IP from any study sites other than those listed on the Form FDA 1572. Investigational product(s) may not be relabeled or reassigned for use by other subjects. If any of the IP is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Each subject will be given enough tubes of study drug to apply up to 1 tube-full (approximately 36 g of clinical trial material) per treatment day until the next study visit. Tubes will be packed 2 to a carton, and each subject will receive enough cartons to have the maximum number of tubes needed until the next study visit. The number of study drug tubes the subject needs to provide enough IP until the next visit is shown in Table 9-2.

Table 9-2: Amount of Study Drug Needed Per Visit

Treatment Period	Number of Cartons	Number of Tubes
Double-blind Treatment Period		
Baseline	3	6
Day 14	4	8
Day 30	6	12
Day 60	6	12
OLE Period		
Day 90	3	6
Day 104	4	8
Day 120	6	12
Day 150	6	12

Each carton will be weighed before dispensing and subjects are to bring all cartons and tubes back at each study visit, whereupon study staff will weigh them again to estimate study drug use and compliance.

Upon completion of the study, the IP (partly used, unused, and empty tubes) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.12. Labeling and Packaging

Labeling and packaging of IP will be performed by Catalent Pharma Solutions, Philadelphia, PA, USA.

Tubes will be packaged in cartons comprising 2 tubes each. Tubes will be labeled with inner and outer booklet labels, and carton number. Each carton will also be labeled with inner and outer booklet labels and numbered.

9.12.1 Labeling

The tubes will have a label affixed that meets the applicable regulatory requirements and may include, but is not limited to, the following: subject identifier, IP name, lot number, protocol number, carton number, caution statement, storage, and sponsor identification.

Save all empty packaging or packaging containing unused tubes for final disposition by the sponsor or contract pharmacy.

Final labeling will comply with the regulatory requirements of each country where the study will be conducted.

9.12.2 Packaging

Investigational products will be packaged in high-density polyethylene, 35 × 100 mm tubes weighing 50 g from which a maximum of 36 g of IP can be extracted. Trifarotene cream HE1 and vehicle will be packaged so as to be blinded to the investigator, the study clinic personnel, and the subjects.

10. STUDY PROCEDURES

Subjects must provide written informed consent and/or assent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

Subjects who agree to participate in the photography and/or PK substudies must provide written informed consent before photographs or serial blood samples are collected.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Events (Section 2.2). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the Schedule of Events for each subject. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

10.1.1 Overall Study Schedule

The overall study duration is expected to be approximately 19 months.

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening and Washout: up to 35 days to comprise washout of excluded medications (Table 9-1).
2. Double-blind Treatment: Twice weekly for 12 weeks.
3. Optional Open-label Extension Treatment: Twice weekly for 12 weeks.
4. Follow-up: 14 days after last study drug application.

The maximum treatment duration for each subject is approximately 12 weeks for subjects who choose not to continue into the open-label extension period, and 24 weeks for those who choose to continue.

The maximum study duration for each subject is approximately 229 days (33 weeks).

10.2. Study Periods and Visits

10.2.1 Screening and Washout

10.2.1.1 Screening Visit (Visit 1)

The subject must be screened within 35 days before randomization in the study. The following procedures will be performed at Screening:

1. Obtain written informed consent and/or assent.
2. Assign a screening number when a subject begins screening.
3. Assess inclusion/exclusion criteria.
4. Collect demographic information.
5. Record medical history, including current therapies (e.g., prescription and nonprescription medications).

6. Perform a physical examination.
7. Measure vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse).
8. Perform a 12-lead ECG.
9. Collect blood and urine for laboratory tests.
10. Perform serum pregnancy test for WOCBP.
11. Record VIIS.
12. Record IGA.
13. Record palm/sole assessment.
14. Record assessment of roughness, and fissuring
15. Record ectropion score.

Procedures for rescreening subjects who initially fail to meet study entry criteria are described in Section 14.3.

10.2.1.2 Washout Period

Excluded medications must be washed over the time periods as shown in Table 9-1. The washout period is part of the 35-day Screening Period.

10.2.2 Double-blind Treatment Period

Eligible subjects who have washed out prohibited medications will be randomized to double-blind study drug.

10.2.2.1 Baseline Visit (Visit 2, Day 1)

The following procedures will be performed on Day 1 in the study clinic:

1. Review inclusion/exclusion criteria.
2. Perform urine pregnancy test for WOCBP.
3. Collect blood and urine for routine laboratory tests (subject must be fasting; i.e., at least 8 hours).
4. Collect a predose PK blood sample (all subjects).
5. Perform physical examination.
6. Record concomitant medications and concomitant therapies.
7. Record VIIS.
8. Record IGA.
9. Record palm/sole assessment.
10. Record assessment of roughness and fissuring.
11. Record ectropion score.

12. Record responses to DLQI and EQ-5D Quality of Life Questionnaires
13. Record vital signs (blood pressure and pulse).
14. Measure and record height, weight, and body mass index (BMI).
15. Perform a 12-lead ECG.
16. Assign randomization number.
17. At sites where the photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
18. Among subjects who consent to participate in the PK substudy, samples will be taken at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1.
19. Clinic staff instructs subject on study drug application, applies initial study drug dose and measures amount used (i.e., study staff will weigh the 50-g tube before and after the first application to determine the fixed dose amount for each subject).
20. Assess and record local tolerance/AEs.
21. Dispense study drug and diaries.
22. Advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.

10.2.2.2 Telephone Visit (Day 7)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.2.3 Visit 3 (Day 14 ±5 days)

The following procedures will be performed on Day 14 in the study clinic:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Assess local tolerance.
4. Record AEs and review diary.
5. Record VIIS.
6. Record IGA.
7. Record palm/sole assessment.
8. Record assessment of roughness and fissuring.
9. Record ectropion score.

10. Record responses to DLQI and EQ-5D Quality of Life Questionnaires
11. Collect a PK blood sample (all subjects).
12. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
13. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.
14. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.

10.2.2.4 Visit 4 (Day 30 ±7 days)

The following procedures will be performed on Day 30 in the study clinic:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Perform a 12-lead ECG.
4. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
5. Collect a PK blood sample (all subjects).
6. Perform a urine pregnancy test for WOCBP.
7. Record AEs and review diary.
8. Assess local tolerance.
9. Record VIIS.
10. Record IGA.
11. Record palm/sole assessment.
12. Assess roughness and fissuring and record findings.
13. Record responses to DLQI and EQ-5D Quality of Life Questionnaires
14. Record ectropion score.
15. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
16. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.
17. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.

18. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.
19. Among subjects who consent to participate in the PK substudy, IP will be applied in the clinic at this visit, and samples will be taken predose and at 1, 2, 4, 8, 12, and 24 hours postdose.
20. Provide information about OLE option.

10.2.2.5 Telephone Visit (Day 45)

Clinic staff will telephone subject to assess safety and to record concomitant medications/therapies. Staff will instruct subject on study drug application, advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary. Staff will remind subject about OLE option.

10.2.2.6 Visit 5 (Day 60 ±7 days)

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Record VIIS.
4. Record IGA.
5. Record palm/sole assessment.
6. Assess roughness and fissuring and record findings.
7. Record ectropion score.
8. Record responses to DLQI and EQ-5D Quality of Life Questionnaires
9. Perform a urine pregnancy test for WOCBP.
10. Collect a PK blood sample (all subjects).
11. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
12. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
13. Record AEs and review diary.
14. Assess local tolerance.
15. Provide information about OLE option.

10.2.2.7 Visit 6 (90 ±7 days) or Early Termination

The following procedures will be performed on Day 90 in the study clinic:

1. Record concomitant medications and concomitant therapies.
2. Perform a physical examination.
3. Record vital signs (blood pressure and pulse).
4. Perform a 12-lead ECG.
5. Collect blood and urine for routine laboratory tests (subject must be fasting at least 8 hours).
6. Collect a PK blood sample (all subjects).
7. Perform a urine pregnancy test for WOCBP.
8. Record AEs and review diary.
9. Assess local tolerance.
10. Record VIIS.
11. Record IGA.
12. Record palm/sole assessment.
13. Assess roughness and fissuring and record findings.
14. Record responses to DLQI and EQ-5D Quality of Life Questionnaires
15. Record ectropion score.
16. Record responses to DLQI and EQ-5D Quality of Life Questionnaires
17. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
18. At sites where the optional photographic substudy is conducted, take photographs of subjects who have provided informed consent for the substudy.

For subjects who successfully complete the initial 12 weeks of double-blind treatment and choose to continue into the OLE, this visit will be the first visit of that portion of the study. All efficacy assessments, safety/tolerability assessments, including clinical laboratory testing, PK from Day 90/Week 12 will be carried over to the OLE Period and will not be repeated. Subjects will have up to 7 days to decide to enter the OLE; if the subject chooses to continue into OLE, the following additional procedures will be done:

1. Have the subject sign OLE-specific informed consent.
2. Measure subject's weight.
3. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.

4. Weigh new study drug tubes and dispense enough additional study drug until next visit (only for subjects who choose to continue into the Open-label Extension).
5. Dispense study diary.

10.2.3 Follow-up Telephone Call (±14 days after Day 90) – Only Subjects Who Do Not Continue into Open-label Extension

Clinic staff will telephone subjects who choose not to continue into the Open-label Extension within 14 days after Day 90 to assess any ongoing AEs.

10.2.4 Open-label Extension

Subjects who complete the 12-week Double-blind Treatment Period of the study may choose to continue into an optional 12-week Open-label Treatment Period with trifarotene cream HE1 200 µg/g. During the OLE Period, subjects will return to the site at Weeks 14, 16, 20, 24, and 26. Additional PK samples will be drawn at Week 16 and 24 from all subjects who continue into the OLE Period.

10.2.4.1 Telephone Visit (Day 97)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and to remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.2 Visit 7 (Week 14; Day 104 ±5 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Assess and record local tolerance/AEs and review diary.
4. Record VIIS.
5. Record IGA.
6. Record palm/sole assessment.
7. Record assessment of roughness and fissuring.
8. Record ectropion score.
9. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
10. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
11. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days

within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit.

10.2.4.3 Visit 8 (Week 16; Day 120 ±7 days)

The following procedures will be performed at this study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Assess and record local tolerance/AEs and review diary.
4. Record VIIS.
5. Record IGA.
6. Record palm/sole assessment.
7. Record assessment of roughness and fissuring.
8. Record ectropion score.
9. Perform a 12-lead ECG.
10. Collect blood and urine for routine laboratory tests.
11. Perform a urine pregnancy test for WOCBP.
12. Collect a PK blood sample (all subjects)
13. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
14. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.
15. Instruct subject on study drug application, and advise subjects regarding permitted emollient(s) for use on nontreatment days; use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited. Remind subjects not to apply IP on visit days until after the visit

10.2.4.4 Telephone Visit (Day 134)

Clinic staff will telephone subject to assess safety (AEs) and to record concomitant medications/therapies. Staff will to instruct subject on study drug application, to advise subjects regarding permitted emollient(s) for use on nontreatment days (use of emollient(s) on study drug treatment days within 4 hours of study drug application is prohibited), and to remind subjects not to apply IP on visit days until after the visit. An unscheduled clinic visit may be performed, if necessary.

10.2.4.5 Visit 9 (Week 20; Day 150 ±7 days)

The following procedures will be performed at each study clinic visit:

1. Record concomitant medications and concomitant therapies.
2. Record vital signs (blood pressure and pulse).
3. Perform a urine pregnancy test for WOCBP.
4. Assess and record local tolerance/AEs and review diary.
5. Record VIIS.
6. Record IGA.
7. Record palm/sole assessment.
8. Record assessment of roughness and fissuring.
9. Record ectropion score.
10. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.
11. Weigh new study drug tubes and dispense enough additional study drug until next visit, and new diary.

10.2.4.6 Visit 10 (Week 24; Day 180 ±7 days) or Early Termination

The following procedures will be performed at Week 24 in the study clinic:

1. Record concomitant medications and concomitant therapies.
2. Perform a physical examination.
3. Record vital signs (blood pressure and pulse).
4. Perform a 12-lead ECG.
5. Collect blood and urine for routine laboratory tests.
6. Perform a urine pregnancy test for WOCBP.
7. Collect a PK blood sample (all subjects)
8. Assess and record local tolerance
9. Record AEs and review diary.
10. Record VIIS.
11. Record IGA.
12. Record palm/sole assessment.
13. Assess roughness and fissuring and record findings.
14. Record ectropion score.
15. Collect returned study drug tubes; confirm study drug compliance by weighing returned tube contents and reviewing diaries.

10.2.4.7 Follow-up Evaluation – Open-Label Period (Week 26/Visit 11)

At 14 days after the last administration of the IP, the following procedures will be performed:

1. Perform a physical examination.
2. Record vital signs (blood pressure and pulse).
3. Record VIIS.
4. Record IGA.
5. Record palm/sole assessment.
6. Assess roughness and fissuring and record findings.
7. Record ectropion score.
8. Perform a urine pregnancy test for WOCBP.
9. Assess and record AEs occurring since the last evaluation and review diary.
10. Record any concomitant medications/therapies.

10.3. Assessments

The VIIS is a valid measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. The VIIS scale was developed to generate a reliable method to assess ichthyosis clinical severity using solely scale and erythema, which are the only findings present in ichthyosis of every genetic cause, and occur either upon skin of normal thickness (lamellar subtypes) or upon thickened skin (keratoderma subtypes).[13] The VIIS uses a 5-point index to assess the level of severity of scale and erythema in each of 4 body areas: chest/abdomen, back, legs, and arms, for a possible overall total of 16 points (Section 10.3.1.1). While retinoid treatment is expected to reduce scale, it may increase erythema; therefore, in this study, erythema will be evaluated as part of local tolerability.

10.3.1 Efficacy Variables

All efficacy measurements will use scales previously used for dermatological studies or as defined in the following sections.

10.3.1.1 Visual Index for Ichthyosis Severity – Scaling

The primary endpoint is the number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/EOT on the overall 16-point VIIS for scaling.

The investigator will rate the subject's condition using the 5-point VIIS for each body area (chest/abdomen, back, legs, and arms) and an overall score at each time point shown in the Schedule of Events (Section 2.2):

0	Clear	Normal skin; no perceptible scale or smoothening
1	Almost clear	Areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
2	Mild	Confluent smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
3	Moderate	Confluent scales (visibly separated/fractured stratum corneum) including some large (>1cm), thick scales
4	Severe	Confluent, primarily large, thick scales

10.3.1.2 Investigator's Global Assessment

The IGA will be measured on a 5-point scale.

0	Clear	No scaling and no roughness, no fissure
1	Almost Clear	Occasional fine scales, hardly palpable roughness (mostly smooth), no fissure
2	Mild	Small and fine scales predominate, no more than a few large scales, mild roughness on palpation, few fissures may be present
3	Moderate	Large rather thick scales predominate, coarse roughness on palpation, few fissures may be present
4	Severe	Large coalescent scales dominate, sharp edges on palpation with plate-like hyperkeratosis, many fissures may be present

10.3.1.3 Palm/Sole Assessment

Thickening of the skin on the palms and soles will be measured on a 5-point scale.

0	Clear	No thickening, no roughness, no fissure
1	Almost Clear	Only slight thickening, minimal to no roughness, no fissures
2	Mild	Some thickening, mild roughness on palpation, few fissures may be present
3	Moderate	Substantial and diffuse thickening, coarse roughness on palpation may be present, fissures may be present
4	Severe	Very thickened and rough skin, numerous fissures

10.3.1.4 Individual Score for Roughness

The amount of roughness of the skin overall will be measured on a 5-point scale.

0	Clear	Smooth skin
1	Almost Clear	Hardly palpably roughness
2	Mild	Mild roughness (fine sand paper-like)
3	Moderate	Moderate, coarse roughness (coarse sand paper-like)
4	Severe	Very coarse skin (broken cornflakes-like)

10.3.1.5 Fissuring Assessment

Fissuring will be assessed by recording the presence or absence of fissures, the number of fissures present, and the pain associated with each fissure. The subject will assess pain associated with fissures as ranging from 0–3 (none, mild, moderate, severe).

10.3.1.6 Dermatology Life Quality Index

The DLQI is a dermatology-specific Quality of Life instrument. It is a simple 10-question validated questionnaire with 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment); higher scores indicate poorer quality of life. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology.

10.3.1.7 EQ-5D Quality of Life Questionnaire

The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the subject's self-rated health on a vertical VAS. This can be used as a quantitative measure of health outcome that reflects the subject's own judgement.

10.3.1.8 Ectropion Severity Score

The Ectropion Severity Score (ESS), has a maximum score of 8 points. A higher score indicates a worse ectropion. The score takes the severity of ectropion in terms of lateral and medial apposition, scleral show, conjunctival show, and roundness of the eye into account and gives an indication of the functional aspects involved in ectropion by scoring redness, excess tear film, and the position of the lacrimal punctum.[14]

10.3.2 Clinical Pharmacology

10.3.2.1 Pharmacokinetic Analysis Methods

The pharmacokinetic characterization of drug concentrations for each dose to be profiled will use noncompartmental analysis (NCA).

10.3.2.2 Pharmacokinetic Parameters

Samples for PK will be drawn from all subjects at Baseline and at each clinic visit for trough values.

Subjects who provide written informed consent to participate in the optional PK substudy will provide blood samples for PK analysis predose on Day 1 and at 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and Day 30.

The PK parameter estimates will be completed using WinNonlin (Pharsight Corporation) software using the actual elapsed times from dose administration to sample collection (i.e., not nominal time).

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area-under-the-curve (AUC) and rate-of-absorption using the maximum concentration (C_{max}) and the time of C_{max} (T_{max}). Additional details of the parameters and their calculation and evaluation will be included in the SAP.

Table 10-1 shows the PK parameters that will be computed for each subject for samples obtained over the planned sampling intervals.

Table 10-1: Pharmacokinetic Parameters

Parameter	Description of Parameter
C_{max}	Maximum (or peak) serum concentration
T_{max}	Time at which C_{max} is observed
$AUC_{(0\text{-}t)}$	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration-time curve from time 0 to infinity (if data permits)
$t_{1/2}$	Apparent first order terminal elimination half-life
λ_z	Apparent terminal phase rate constant (if data permits)

10.3.3 Sample Collection

Samples will be collected at the time points specified in the Schedule of Events (Section 2.2). Specimen preparation, handling, shipment, and storage for the complete blood count, chemistry, and urinalysis are described in the study laboratory manual.

Blood

Each blood sample will be 3 mL/kg in volume. The total amount of blood to be drawn for serial PK assessments will be a maximum of 5 mL/kg per subject over a 24-hour period.

Urine

Urinalysis will be performed at central laboratory. Dipstick and urine pregnancy tests will be conducted on site.

10.3.4 Safety Variables

Safety assessments will include the evaluation of AEs, including local tolerability (stinging/burning, pruritus, and erythema), clinical laboratory assessments, vital signs, 12-lead ECGs, and physical examinations.

10.3.4.1 Clinical Laboratory Safety Assessments

10.3.4.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 2.2).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides
Coagulation Panel:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones
Pregnancy Test:	for women of childbearing potential only; serum at Screening, urine at each other visit.
Serology	Hepatitis B surface antigen, and hepatitis C

All blood samples for the clinical laboratory tests must be taken in a fasting state, at least 8 hours after the previous drug application.

Blood and urine samples for hematology, and serum chemistry will be sent to a central laboratory for analysis. Urine pregnancy tests and dipstick will be conducted at the study sites.

10.3.4.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are packed and shipped appropriately according to the applicable regulations.

Samples for assessment of clinical laboratory tests will be transported to Clinical Reference Laboratory (see the study laboratory manual for addresses).

10.3.4.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Mayne Pharma LLC prior to beginning the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically significant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical significance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically significant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.4.2 Clinical Examinations

10.3.4.2.1 Vital Signs

Vital signs, including height and weight (only assessed at Screening), blood pressure and pulse will be measured.

10.3.4.2.2 Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. All ECG recordings will be identified with the subject number, date, and time of the recording.

10.3.4.2.3 Physical Examination

A complete physical examination excluding the genitourinary examination will be performed as indicated in the Schedule of Events (Section 2.2).

10.3.4.2.4 Other Safety Variables

Local tolerability will be assessed on a 0–3 scale (none, mild, moderate, severe). All application site reactions will be recorded as AEs.

10.3.4.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in subjects treated with control product are also considered AEs.

11.1.2 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADRs).

The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IP qualify as ADRs.

All AEs for which the judgment of relationship to IP is "possible" or higher will be considered ADRs. If a relationship to IP is not provided, then the AE must be treated as if it were "possible."

11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the known AE profile of the product. For a preapproval test product, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure [IB] for an unapproved investigational product or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events.

11.1.4 Serious Adverse Events/Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6 Treatment-Emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first application of IP (trifarotene or vehicle) and not more than 14 days after the last application of IP.

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review by a study monitor.

All reported AEs, including local and systemic AEs not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All reported AEs occurring while on study must be documented appropriately regardless of relationship. All reported AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of a reported AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study clinic personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 14 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs. In addition, although local tolerability will be assessed on a 0-3 scale, all application site reactions should be recorded as AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as follows:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3 Action(s) Taken

All AEs will be treated/managed according to standard practice. The following actions may be taken with regard to the IP. Section 9.4 describes dose adjustment and stopping rules for individual subjects.

Action(s) taken may consist of the following:

Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome of an AE at the time of last observation will be classified as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	An AE with sufficient evidence to accept that there is no causal relationship to IP administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven.)
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to IP administration that makes a causal relationship improbable, and in which other drugs, events, or underlying disease provide plausible explanations.
Possibly related	An AE with a reasonable time sequence to administration of the IP, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Related	An AE occurring in a causal plausible time relationship to IP administration that cannot be attributed to a concurrent disease or other drugs, chemicals, or events. The AE relationship to the IP must be assessed separately by the investigator and Mayne Pharma LLC.

11.2.3 Documentation

All AEs that occur within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)

- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP(s)

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject may be withdrawn for treatment but continue to be followed for efficacy and safety in the study. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

It is not necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

Any AE will be followed (up to a maximum of 14 days after the last dose of IP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to Premier Research within 24 hours of first becoming aware of the event by e.g., completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the Premier Research by one of the following methods:

Email: globalPV-US@premier-research.com

Email: PVDS-ROW@premier-research.com

Fax number: +1 215 972 8765

Fax number: +421 2 6820 3713

This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Subject's study number
- Subject's year of birth
- Subject's gender
- Date of first dose of IP(s)
- Date of last dose of IP(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s) ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial report, adverse event, date of occurrence, subject identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the Premier Research Pharmacovigilance Department using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of his or her health authorities, institutional review board (IRB)/independent ethics committee (IEC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.2 Adverse Drug Reactions

All ADRs should be reported by the investigator in the eCRF.

Suspected serious ADRs must be reported to the sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.3 Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported by Premier Research to Mayne Pharma LLC in aggregate monthly status reports.

11.3. Special Considerations

11.3.1 Adverse Events of Special Interest

Since topical retinoids are associated with local application site AEs, particularly when beginning treatment, these events will be followed closely during the study and considered AEs of special interest (AESIs).

11.3.2 Pregnancy

All WOCBP who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during IP treatment will be immediately discontinued from study treatment. The investigator must report the pregnancy of any woman who becomes pregnant during or within 30 days after discontinuing treatment as if it were an SAE within 24 hours of learning of the pregnancy, to Premier Research Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on an SAE and AE form (entering the event temporarily as nonserious on both forms) provided by the sponsor or its designee. If a partner of a male study subject becomes pregnant, the investigator must report the pregnancy as soon as possible after learning of it to the Premier Research Pharmacovigilance using the Pregnancy Data Collection Form. A separate pregnant partner ICF will be required.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy in a study subject. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

12. DATA SAFETY MONITORING BOARD

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including LI. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate under a charter that will be finalized prior to the start of the study. The DSMB will meet at least 3 times during the conduct of the study: when the study begins, when 15 adult subjects have enrolled in Cohort A and have completed at least 28 days of treatment, and after 60 subjects have enrolled in the study.

The DSMB will meet after subjects in Cohort A have completed at least 28 days of double-blind treatment to review aggregate safety and tolerability data. The data will remain blinded unless an issue or trend arises that requires unblinding. At that time, the DSMB will decide whether Cohort B (adults and subjects aged 12–17) may begin enrolling. The DSMB will have the authority to recommend to the sponsor that the study be placed on hold or discontinued if serious safety issues are discovered. The DSMB will provide its input to Mayne Pharma LLC.

In case of significant toxicity, the DSMB may choose to review the available safety data and recommend stopping recruitment in a particular dose group. If toxicity is observed, the treatment assignment for the subject(s) involved may be unblinded by the DSMB at its discretion.

Stopping rules for individual subjects are in Section 9.4.1.

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. A SAP that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a P value of ≤ 0.05 will be considered statistically significant.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will include the number and percentage of subjects in each category.

The primary analysis period is the first 12 weeks of treatment (i.e., the Double-blind Period). Overall unblinding will take place at the end of the Double-blind Period of the study only after the database is locked. A second analysis will take place for endpoints assessed from Week 12 through the OLE Period. The baseline for the safety and efficacy parameters will be measured at Visit 1 or Visit 2, per the Schedule of Events for both the Double-blind (Table 2-1) and OLE (Table 2-2) Periods.

13.1.1 Analysis Populations

The following 5 analysis populations are planned for the Double-blind Period of this study:

- Safety: all subjects who are randomized to treatment and receive at least 1 application of study drug in the Double-blind Period. This population will be the primary population for analyses of safety.
- Intent-to-treat (ITT): all randomized subjects.
- Modified intent-to-treat (mITT): all subjects in the safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period.
- Per-protocol (PP): subjects in the mITT Population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application, and who had no significant protocol deviations.
- Pharmacokinetic: all subjects in the Safety Population who have at least 1 plasma sample with quantifiable concentration. This population will be used to summarize all PK endpoints.

The following analysis populations are planned for the OLE Period of this study:

- OLE Safety: all subjects who complete the 12-week Double-blind Treatment Period and receive at least 1 application of study drug in the OLE Period.
- OLE ITT: all subjects who complete the 12-week Double-blind Treatment Period and sign the OLE informed consent.
- OLE mITT: all subjects in the OLE safety population with at least 1 assessment of efficacy after Visit 6.

- OLE PP: all subjects in the OLE mITT population who met all inclusion criteria and no exclusion criteria, were compliant with study drug application from baseline through EOT, and who had no significant protocol deviations throughout the study.

Inclusion in the analysis populations will be determined prior to database lock.

If a subject is randomized incorrectly or is administered the incorrect IP, analyses of the ITT and mITT populations will be based on the assigned treatment whereas all other analyses will be based on the actual treatment received.

13.1.2 Study Subjects and Demographics

13.1.2.1 Disposition and Withdrawals

For the Double-blind Period, the numbers of subjects randomized, completing Week 12 of the study, and withdrawing early from the Double-blind Period, along with reasons for withdrawal, will be tabulated overall and by randomized treatment group. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated by randomized treatment group. This analysis will be conducted for the ITT population.

For the OLE Period, the number of subjects entering the OLE Period, completing the study, and withdrawing early, along with reasons for withdrawal, will be tabulated overall. The number of subjects in each analysis population will be reported. The number of subjects completing study milestones will also be tabulated. This analysis will be conducted for the OLE ITT population.

13.1.2.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations promptly. All deviations must be addressed in study source documents, and reported to Premier Research or Mayne Pharma LLC. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

13.1.2.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for the ITT and OLE ITT populations.

Demographic variables will include age, sex, race, ethnicity, height, weight, and BMI. Baseline subject characteristics will include medical history, physical examination findings, and VIIS score.

Prior and concomitant medications will be summarized by randomized treatment group, by the number and percentage of subjects taking each medication, and classified using World Health

Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of each subject's dose, and in terms of duration of exposure for each period. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group. Additionally, the number of subjects who are compliant with investigational product will be presented by treatment group for the Double-blind Period and overall for the OLE.

13.1.4 Efficacy Analysis

The mITT population will be used as the primary population for the primary analysis of efficacy at Week 12. All efficacy analyses will be repeated as secondary analyses in the ITT and PP populations for the Double-blind Period. Efficacy analyses will also be repeated in the OLE Period using the OLE mITT and OLE PP populations. No formal inferential analyses will be conducted for efficacy variables in the OLE Period.

13.1.4.1 Efficacy Endpoints

Primary efficacy endpoint: The number of subjects in each treatment group who experience successful resolution of LI where "success" is defined as clear/almost clear overall and at least a 50% reduction from Baseline at Week 12/ EOT in the Double-blind Period on the overall 16-point VIIS for scaling (i.e., 0-4 points on each of the 4 body areas: chest/abdomen, back, arms, and legs).

Secondary: The secondary endpoints are as follow:

- The difference in mean scores between the active trifarotene cream HE1 and vehicle groups in the following assessment indices:
  - IGA (Scale: 0-4) for each body area
  - Palm/sole Assessment (Scale: 0–4)
  - Individual score for roughness (Scale: 0–4) overall
- The difference in proportion of subjects with presence of fissures (presence/absence, number of fissures, and pain associated with fissures [on a 0-3 scale]) between the active trifarotene cream HE1 and vehicle groups
- Quality of life per Dermatology Life Quality Index (DLQI)

Exploratory: The exploratory endpoints are as follow:

- The difference in mean ectropion scores (ESS of 0–8) between the active trifarotene cream HE1 and vehicle groups
- Quality of life per EQ-5D-5L

13.1.4.2 Primary Analysis

For the Double-blind Period only, the number and proportion of subjects in each treatment group with successful resolution of LI by Week 12/EOT will be presented along with the difference in

proportions between each trifarotene cream HE1 group and vehicle. 95% confidence intervals (CI) will be provided for proportions. Generalized estimating equations (GEE) for binary response will be used to model the odds of successful resolution of LI with treatment group as a predictor. Other covariates, such as baseline VIIS scores, baseline characteristics, and interactions may be included. Various correlation matrix structures will be explored to model the within subject correlation. Additionally, the difference in mean VIIS score at Week 12/EOT between the active trifarotene cream HE1 groups and vehicle group will be analyzed using a 2-sided, 2-sample Wilcoxon rank-sum test at the 5% significance level. The null hypothesis is that the mean of each trifarotene cream HE1 group is equal to the mean of the vehicle group.

Descriptive summaries (such as mean, standard error, median, minimum, and maximum) and the changes from baseline will be provided for VIIS scores for both periods.

13.1.4.3 Secondary Analyses

Secondary and exploratory efficacy endpoints will be analyzed separately for each period (Double-blind and OLE) using descriptive statistics.

Additionally, for the Double-blind Period only, change from Baseline through Week 12 will be presented and analyzed using a mixed model for repeated measures (MMRM). The model will include the change from baseline score as the dependent variable, treatment group as a fixed effect, subject as a random effect, and baseline score value as a covariate. Frequencies of results and 95% CIs will also be reported and scores will be analyzed as categorical variables using the Cochran-Mantel-Haenszel test.

For subjects who report having fissures, descriptive summaries of the number of fissures and pain related to fissures will also be presented by treatment group and body area for each period.

The DLQI scores will also be analyzed using descriptive statistics through Week 12.

13.1.4.4 Exploratory Analyses

Descriptive summaries and the changes from baseline will be provided for ectropion scores and EQ-5D-5L scores by visit for each period. No formal inferential analyses will be conducted for exploratory endpoints.

13.1.4.5 Corroborative, Sensitivity, and Other Analyses

To assess the effect of missing data on the primary efficacy analysis, a sensitivity analysis will be performed using LOCF for the Double-blind Period only. Imputation will not be performed in the OLD period.

For analyses involving study site, if the number of subjects per site is small, sites may be pooled for safety and efficacy analysis or omitted from statistical models as the anticipated number of subjects per site is small, treatment is self-administered, and the sites are using standardized procedures for all assessments. If the distribution of enrollments at sites is such that one or few are enrolling a majority of subjects, a subgroup analysis by site may be performed. The final determination will be made prior to database lock.

Details of these analyses will be further detailed in the SAP.

13.1.5 Clinical Pharmacology Analyses

13.1.5.1 Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics. Descriptive statistics reported will include the arithmetic mean, SD, CV%, geometric mean, minimum, maximum, and median. Only the range and the median will be reported for Tmax, as this is a categorical parameter. The PK parameters will also be summarized by treatment using descriptive statistics.

Individual plasma concentration plots and mean data graphs will be produced using both linear and semi-logarithmic scales. Mean data graphs will show plasma concentration profiles by treatment group.

Pharmacokinetic plasma parameter estimates and summaries will be completed for the subjects in the PK population. Testing of PK parameters will be outlined in the SAP.

13.1.6 Safety and Tolerability Analyses

Safety analyses through Week 12 of the Double-blind Period will be conducted using data from the Safety Population and safety analyses in the OLE Period will be conducted using the OLE Safety Population (as defined in Section 13.1.1). Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, and physical examination results. No formal inferential analyses will be conducted for safety variables in either period.

13.1.6.1 Local Tolerability

During all clinic visits, the investigator will assess local tolerability (Scale: 0–3 [none, mild, moderate, severe]) on each of the 4 body areas (chest/abdomen, back, legs, arms). Descriptive summaries will be presented by period, treatment group, and visit.

13.1.6.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1 or higher.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first, or
- AEs starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with IP through the Follow-up Visit or Early Termination Visit, whichever occurs first.

The number and percentage of subjects with AEs will be displayed by each treatment group in the Double-blind Period and overall in the OLE by system organ class and preferred term. Summaries of AEs by severity and relationship to IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.6.3 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values for each treatment group at each time point in each period.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory parameter by treatment group and by study visit in each period.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.1.6.4 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse for each period.

The number of subjects with vital signs values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each parameter by period, by treatment group and by study visit. Pre and post-treatment values may also be presented with an analysis of mean changes from baseline.

13.1.6.5 Twelve-lead Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point in each period. Abnormal results will be grouped as clinically significant and not clinically significant.

A comparison of QT results will be presented. Summary statistics will be displayed by period, by treatment group, and by visit for QT and the QT interval corrected for heart rate (QTc) calculated using Fridericia's QT correction methods.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTcF interval (Fredericia's correction methods), and HR for each treatment group at each time point in each period.

13.1.6.6 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group in each period.

13.1.7 Interim Analysis

No interim analyses are planned.

13.2. Sample Size Determination

Accounting for a 20% drop-out/nonevaluable rate, a total sample size of 120 subjects randomized in a 1:1:1 ratio to 2 active trifarotene cream HE1 arms and a vehicle cream arm will provide >80%

power to detect a difference between each separate trifarotene cream HE1 arm (32 evaluable subjects) and the vehicle cream arm (32 evaluable subjects) using a 2-sample t-test assuming a mean difference of at least 1.0 and a standard deviation of 1.4 or lower. This study is not powered to detect a difference between the 2 active arms.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6 for US studies/Section 14.6.1 for studies conducted outside of the US).

Mayne Pharma LLC agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 18.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The trial will be conducted in accordance with ICH GCP, and the applicable United States (US) Code of Federal Regulations (CFR). The principal investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP training.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IP(s), and their specific duties within the context of the study. Investigators are responsible for providing Mayne Pharma LLC with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all

documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Premier Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Premier Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Premier Research

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory/GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening Visit. If a subject is eligible to enter the study after having previously failed screening, the subject will be assigned a new subject identification number.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

14.4. Study Documents

All documentation and material provided by Mayne Pharma LLC for this study are to be retained in a secure location and treated as confidential material.

14.4.1 Informed Consent

Consent and assent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The informed consent and assent forms are submitted with this protocol.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent and assent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent and assent forms and ask questions before signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate. The participant will sign the informed consent or assent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent and assent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date) and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.4.2 Investigator's Regulatory/Good Clinical Practice Documents

The regulatory/GCP documents are listed below.

- Signed original protocol (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and subinvestigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form Signature Log/Delegation of Study-related Duties
- Approved ICF and subject materials
- FDA1572 and financial disclosure forms, as applicable (US sites)
- Any other relevant GCP documents

The regulatory/GCP documents must be received from the investigator and reviewed and approved by Mayne Pharma LLC or its designee before the study site can initiate the study and before Mayne Pharma LLC will authorize shipment of IP to the study site. Copies of the investigator's regulatory/GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the trifarotene (CD5789) Cream IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and IP accountability records should also be retained as part of the investigator's regulatory/GCP documents. It is the investigator's responsibility to ensure that

copies of all required regulatory/GCP documents are organized, current, and available for inspection.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.5. Data Quality Control

Mayne Pharma LLC and its designees will perform quality control checks on this clinical study.

14.5.1 Monitoring Procedures

Mayne Pharma LLC and/or its designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Mayne Pharma LLC personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures

- storage and accountability of IP and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF will be provided to the sites. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Mayne Pharma LLC or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

For additional information, please refer to the clinical monitoring plan (CMP).

14.5.2 Data Management

Mayne Pharma LLC or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and Premier Research's standard operating procedures. A comprehensive data management plan (DMP) will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries will be provided to the sites.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Mayne Pharma LLC or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or clinical study report [CSR])

Mayne Pharma LLC or its designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Mayne Pharma LLC immediately.

14.6. Study Termination

The study may be terminated at Mayne Pharma LLC's discretion at any time and for any reason.

The DSMB may recommend discontinuation of the study if they find evidence of unacceptable risk to subjects.

14.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, Mayne Pharma LLC or designee will notify the IECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

14.6.2 Premature Study Termination

The study may be temporarily suspended or terminated prematurely if there is sufficient reasonable cause at any time by Mayne Pharma LLC, IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Mayne Pharma LLC or its designee will notify the IECs and regulatory authorities about the premature termination as required according to national laws and regulations. Mayne Pharma LLC or its designee must clearly explain the reasons for premature termination.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the IND or IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is terminated prematurely, all investigators have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Follow-up Visit.

The study might resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or FDA.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. Mayne Pharma LLC may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.7.1 Record Retention

For sites in the US, the investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until 1 of the following occurs:

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

Outside of the US, after completing the study, Mayne Pharma LLC will receive the original eCRFs or at least a legible copy and retain the documents for at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

14.7.2 Sample Retention

Blood samples will be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made

that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

Data collected for this study will be analyzed and stored at Premier Research.

14.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Mayne Pharma LLC. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

14.9. Use of Information and Publication

All information concerning trifarotene (CD5789) cream HE1, Mayne Pharma LLC's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Mayne Pharma LLC or its designee to the investigator, and not previously published, is considered confidential and remains the sole property of Mayne Pharma LLC. Case report forms also remain the property of Mayne Pharma LLC. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by Mayne Pharma LLC in connection with the continued development of trifarotene (CD5789) cream HE1 and thus, may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Mayne Pharma LLC. Publication or other public presentation of trifarotene (CD5789) cream HE1 data resulting from this study requires prior review and written approval of Mayne Pharma LLC. Abstracts, manuscripts, and presentation materials should be provided to Mayne Pharma LLC for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until Mayne Pharma LLC has reviewed and commented on such a presentation or manuscript for publication. If applicable, this study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

15. FINAL CLINICAL STUDY REPORT

Mayne Pharma LLC will retain ownership of the data.

The final CSR will be written within 1 year of completion of the clinical part of the study. For pediatric studies, the final CSR will be written within 6 months. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR may be submitted to the regulatory authorities.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

16.2. Subject Information and Informed Consent and/or Assent

A properly constituted, valid IRB or IEC must review and approve the protocol, the investigator's ICF, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent and/or assent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, subjects must provide their written informed assent or consent prior to enrollment in a clinical study and before any protocol-specified procedures are performed. Subjects must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent and/or assent as described in the Declaration of Helsinki and will also comply with local regulations.

Each subject should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The written information must be provided to the subject to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent. The investigator must confirm that the text was understood by the subject. The subject will then sign and date the IRB/IEC-approved consent form indicating that he or she has given his or her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study subject number. Each subject's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Mayne Pharma LLC, and/or the sponsor's designee. Collection of informed consent and/or assent has to be documented in the eCRF.

Furthermore, the subject will be informed that if he or she wishes to dropout or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Subjects may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Subjects will be asked to agree to a final assessment in the event of an early termination of the study.

Subjects will be informed that data from their case may be stored in a computer without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory

authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

16.3. Approval by Institutional Review Board and Independent Ethics Committee

A valid IRB/IEC must review and approve this protocol before study initiation. Written notification of approval is to be provided by the investigator to the sponsor's or the sponsor's representative before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must follow local country requirements.

Until written approval by the IRB/IEC has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by Mayne Pharma LLC before implementation.

16.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

17. REFERENCES

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18. ATTACHMENTS

18.1. Investigator's Agreement

PROTOCOL NUMBER:	18-ICH-001
PROTOCOL TITLE:	A Phase 2 Randomized, Multi-center, Double-blind, Vehicle-controlled, 12-Week, Safety, Efficacy, and Systemic Exposure Study followed by a 12-Week Open-label Extension of Trifarotene (CD5789) Cream HE1 in Adults and Adolescents with Autosomal Recessive Ichthyosis with Lamellar Scale
FINAL PROTOCOL DATE:	28-Nov-2018

The undersigned acknowledges possession of and has read the product information on the IP and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected subjects in his/her care, according to the study protocol.

He or she agrees to use the study material, including IP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Mayne Pharma LLC.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Mayne Pharma LLC within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IP.

He or she agrees to comply with Mayne Pharma LLC and regulatory requirements for the monitoring and auditing of this study.

In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

APPENDICES

A. Regulations and Good Clinical Practice Guidelines

A. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives (and applicable regulations/guidances):

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents>

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf