Sponsor	Mayne Pharma
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
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Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
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Document History

Reasons for Version Final 2.0

The protocol was amended to version 3.0, and this SAP reflects changes in the protocol.

Text was added to inform of the study being terminated by Mayne Pharma.

Summary of Non-Administrative Changes

- Globally, all references to “Week X” were changed to “Day XX”; e.g., “Week 12” was changed to “Day 90”.
- Figures 1 and 2 (Double-blind and Open-label study designs, respectively) were updated according to protocol changes.
- The Schedule of Events was updated, including the addition of coagulation laboratory panel.
- The lower limit for Analysis Visit 1 was updated to be -97.
- Table 8 (Ectropion Scoring) was updated to add a maximum score.
- The derivation of treatment emergent adverse event was updated to match the protocol, with the upper limit of the start of the event being at most 14 days after last application of study drug.

Table of Contents

Approvals 1
Document History 2
Table of Contents 3
List of Tables 5
List of Figures 5
1. Overview 6
2. Study Objectives and Endpoints 6
2.1. Study Objectives 6
2.1.1. Primary Objective 6
2.1.2. Secondary Objectives 6
2.2. Study Endpoints 7
2.2.1. Safety Endpoints 7
2.2.2. Efficacy Endpoints 7
2.2.3. Pharmacokinetic Variables 7
3. Overall Study Design and Plan 8
3.1. Overall Design 8
3.2. Sample Size and Power 10
3.3. Study Population 10
3.4. Treatments Administered 10
3.5. Method of Assigning Subjects to Treatment Groups 11
3.6. Blinding and Unblinding 11
3.7. Schedule of Events 11
4. Statistical Analysis and Reporting 18
4.1. Introduction 18
4.2. Interim Analysis and Data Monitoring 18
5. Analysis Populations 19
6. General Issues for Statistical Analysis 20
6.1. Statistical Definitions and Algorithms 20
6.1.1. Baseline 20
6.1.2. Adjustments for Covariates 20
6.1.3. Multiple Comparisons 20
6.1.4. Handling of Dropouts or Missing Data 20
6.1.5. Analysis Visit Windows 21
6.1.6. Pooling of Sites 21
6.1.7. Derived Variables 21
6.1.8. Data Adjustments/Handling/Conventions 22

7. Study Subjects and Demographics 24
7.1. Disposition of Subjects and Withdrawals 24
7.2. Protocol Violations and Deviations 24
7.3. Demographics and Other Baseline Characteristics 24
7.4. Exposure and Compliance 25
8. Efficacy Analysis 25
8.1. Primary Efficacy Analysis 25
8.1.1. Investigator's Global Assessment (IGA) 25
8.1.2. Multiple Imputation 27
8.2. Secondary Efficacy Analyses 28
8.2.1. Visual Index for Ichthyosis Severity (VIIS) 28
8.2.2. Individual Score for Roughness 30
8.2.3. Palm/Sole Assessment 31
8.2.4. Quality of life per Dermatology Life Quality Index (DLQI) and Children's DLQI (cDLQI) 32
8.2.5. Fissures 33
8.3. Exploratory Efficacy Analyses 33
8.3.1. Ectropion 33
8.3.2. Quality of Life per EQ-5D-5L and EQ-5D-Y 34
9. Safety and Tolerability Analysis 34
9.1. Adverse Events 35
9.1.1. Adverse Events Leading to Withdrawal 35
9.1.2. Deaths and Serious Adverse Events 36
9.2. Clinical Laboratory Evaluations 36
9.3. Vital Signs 36
9.4. Electrocardiograms 36
9.5. Local Tolerability 37
9.6. Physical Examination 37
9.7. Concomitant Medication 37
9.8. COVID-19 Visit Impact 37
10. Changes from Planned Analysis 37
11. Other Planned Analysis 38
11.1. Pharmacokinetic Analysis 38
11.2. Photography 39
12. References 39
13. Tables, Listings, and Figures 39
13.1. Planned Table Descriptions 40
13.2. Efficacy Data 41

13.3. Safety Data 44
13.4. Pharmacokinetic Data 47
13.5. Planned Listing Descriptions 47
13.6. Planned Figure Descriptions 48
14. Tables, Listings, and Listing Shells 50
14.1. Standard Layout for all Tables, Listings, and Figures 50
14.2. Planned Table Shells 52
14.3. Planned Listing Shells 111
14.4. Planned Figure Shells 146
Appendix 1: Premier Research Library of Abbreviations 147

List of Tables

Table 1: Schedule of Events for Double-blind Period 12
Table 2: Schedule of Events for Open-label Extension 16
Table 3: Analysis Visit Windows 21
Table 4: IGA Scoring Definitions 25
Table 5: VIIS Scoring Definitions 28
Table 6: Roughness Scoring Definitions 30
Table 7: Palm/Sole Scoring Definitions 31
Table 8: Ectropion Scoring 33
Table 9: Demographic Data Summary Tables and Figures 41
Table 10: Efficacy Data 41
Table 11: Safety Data 44
Table 12: Pharmacokinetic Data 47
Table 13: Planned Listings 47
Table 14: Planned Figures 49

List of Figures

Figure 1: Double-blind Study Design 9
Figure 2: Open-label Study Design 10
Figure 3: Standardized Layout 51
Figure 4: Planned Table Shells 53

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Mayne Pharma protocol number 18-ICH-001 (A Phase 2 Randomized, Multi-center, 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), version 3.0 dated 26-Oct-2020. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials.[1] All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society,[3] for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

Upon sponsor discretion, this study was terminated before the study completed enrollment; however, all planned analyses will still occur. Sixty-five (65) subjects were enrolled in the study before termination. The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Mayne Pharma's study 18-ICH-001.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. 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.

2.1.2. Secondary Objectives

The secondary objectives are:

- 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.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Reported serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and changes in clinical laboratory tests, vital signs, physical examinations, and 12-lead electrocardiograms (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).

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is 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 Investigator Global Assessment (IGA) full body scale.

2.2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- 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) 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 Day 90 between the active trifarotene cream HE1 and vehicle groups

2.2.2.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints of this study include the following:

- 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

2.2.3. Pharmacokinetic Variables

The pharmacokinetic (PK) endpoints of the study include plasma concentrations of CD5789 and its major metabolites.

3. Overall Study Design and Plan

3.1. Overall 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 90 days.

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 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.

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 90 days in the same manner as subjects in Cohort A. All subjects (Cohort A and Cohort B) 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 in the OLE will receive open-label trifarotene cream HE1 200 µg/g twice weekly for up to 90 days. A schematic of each period is provided in Figure 1 and Figure 2.

Figure 1: Double-blind Study Design

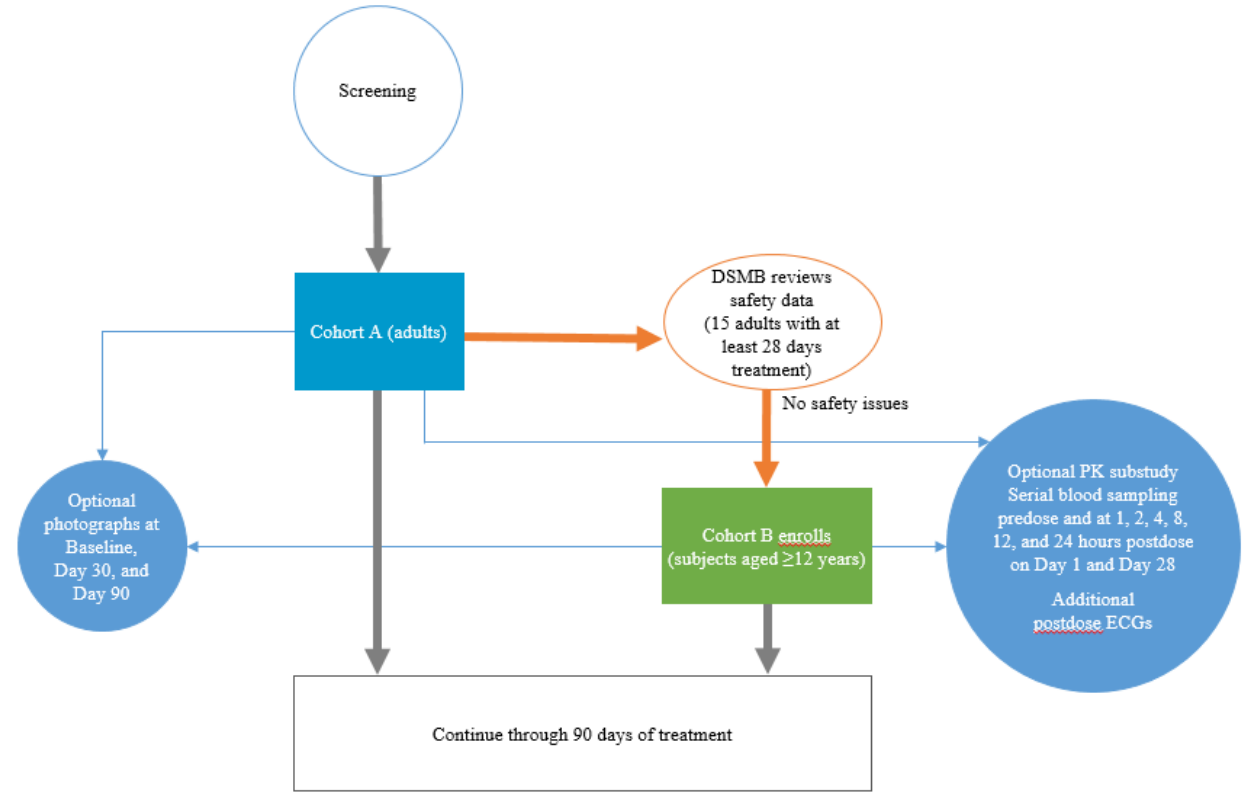
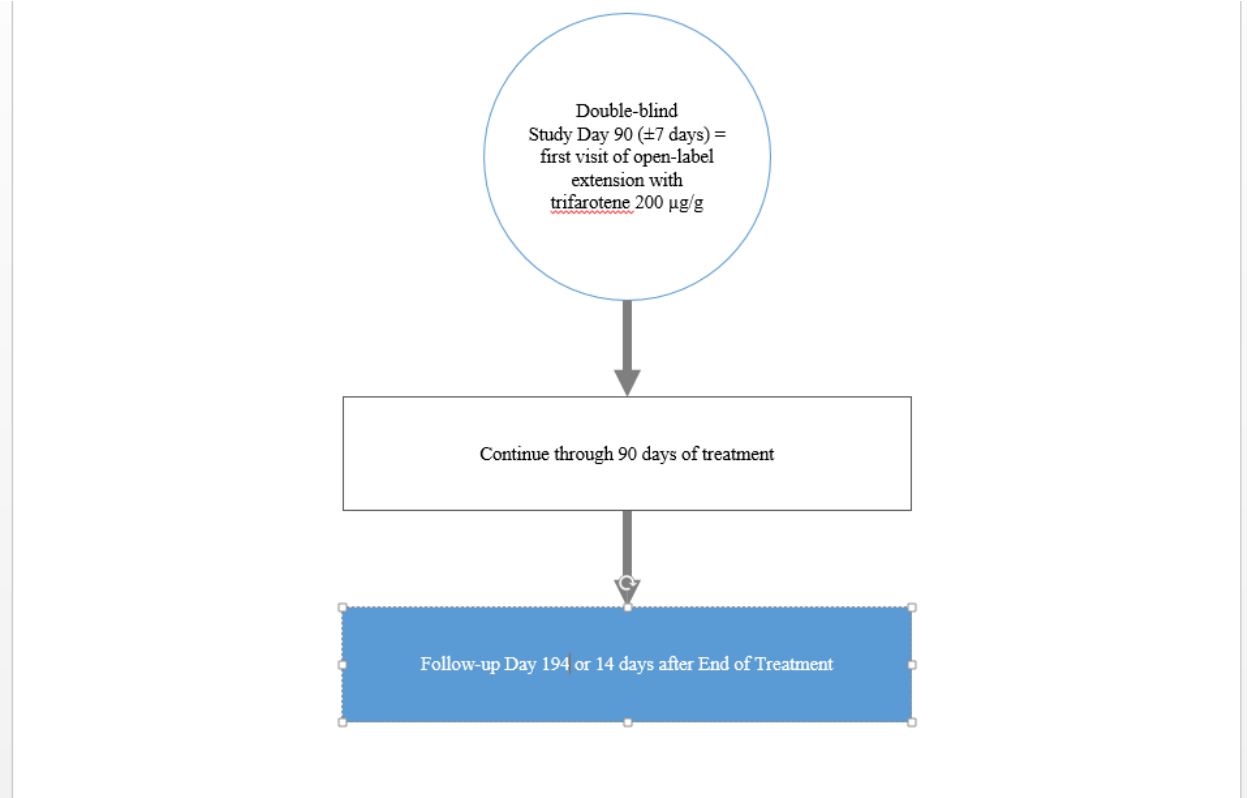


Figure 2: Open-label Study Design



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.

3.3. Study Population

This study includes adults and adolescents with moderate to severe autosomal recessive ichthyosis with lamellar scale.

3.4. 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% body surface area (BSA) of each subject. Trifarotene cream HE1 is a cream containing 100 or 200 µg/g (0.01% [w/w] or 0.02% [w/w], respectively) of CD5789. 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 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.

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 90 days.

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.

3.5. Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1:1 ratio to trifarotene cream HE1 100 µg/g or 200 µg/g or vehicle cream in the Double-blind Period.

Subjects who continue into the OLE 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 90 days.

3.6. Blinding and Unblinding

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 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.

3.7. Schedule of Events

A detailed schedule of events for the Double-blind period of the study is provided in Table 1. A detailed schedule of events for the OLE is provided in Table 2.

Table 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[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
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 ofcare 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 studykits (tubes and boxes, but not leaflets) and reviewing diary.

Table 2: Schedule of Events for Open-label Extension

	Open-label Treatment Period[a]						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[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
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

	Open-label Treatment Period[a]						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[a]**	**8[a]**		**9[a]**	**10[a]**	**11[a]**
Tolerability assessment		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	

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). Measure study drug tubes before dispensing. 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.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with nonmissing values, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with nonmissing data at each study visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD, SE) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified and with the following exceptions: a percentage of 0% will not be displayed (i.e., only the count of 0 will be displayed), and a percentage of 100% will be displayed with 0 decimal places.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and *P* values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests. A *P* value of ≤0.10 but >0.05 will be considered evidence of a trend.

4.2. Interim Analysis and Data Monitoring

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 concentration data, PK parameters, 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 meet again after 60 subjects have enrolled in the study. The sponsor may request additional reviews, e.g., should any other findings/issues pertaining to safety emerge requiring DSMB review. Details of the DSMB operation will be developed in conjunction with the members of the DSMB before the first meeting and will be modified as required. The unblinded DSMB outputs will not be seen by anyone except the DSMB and the performing statistician.

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. The data will be cleaned and frozen and an unblinded analysis of the data will be performed. The data will be considered final at this point and no changes to these data will be permitted following unblinding with the exception of outcomes and end dates of ongoing AEs and concomitant mediations. A second analysis will take place for endpoints assessed from Day 90 through the OLE.

The protocol assumes a 20% dropout/non-evaluable rate. This rate will be continuously monitored throughout the COVID-19 pandemic. In the event that this rate dramatically increases, a blinded sample size reestimation may be performed to ensure statistical power for the primary endpoint is maintained using the assumptions in Section 3.2.

5. 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. Subjects will be analyzed by actual treatment received.
- **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. Subjects will be analyzed by randomized treatment.
- **Modified intent-to-treat (mITT)**: all subjects in the Safety population with at least 1 postbaseline assessment of efficacy in the Double-blind Period. Subjects will be analyzed by randomized treatment.
- **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. Subjects will be analyzed by actual treatment received.
- **Pharmacokinetic (PK)**: 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. Subjects will be analyzed by actual treatment received.

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.

Since all subjects in the OLE are to receive trifarotene cream HE1 200 µg/g, analyses will be by actual treatment received.

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.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last nonmissing assessment recorded prior to the first dose of treatment in the Double-blind Period will be used as the baseline observation for all calculations of change from baseline, including those in the OLE.

6.1.2. Adjustments for Covariates

If there is a statistical difference among treatment groups with respect to baseline characteristics, that variable may be added to the statistical models as a blocking factor or covariate to determine the effect on treatment. Age group and baseline score are planned for inclusion in statistical models, unless otherwise indicated. Age group will be categorized as adolescents (ages 12 to 17 years, inclusive) and adults (≥18 years).

6.1.3. Multiple Comparisons

No adjustments will be made for multiple comparisons. All *P* values for the secondary and exploratory endpoints will be provided in the summary tables for informational purposes only.

6.1.4. Handling of Dropouts or Missing Data

All possible efforts will be made to ensure that subjects stay in the study and all data are collected as scheduled. 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.

Missing endpoint values in this study may result from subjects discontinuing from the study prematurely or missing intermediate assessments while remaining on study. 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 vehicle treatment. The IGA scores will be imputed and then categorized as treatment success.

Sensitivity analyses to investigate robustness to missing data will be performed for the primary endpoint as described in Section 8.1.2.

Missing safety data and data for secondary endpoints will not be imputed.

6.1.5. Analysis Visit Windows

Visits will be analyzed as scheduled. Unscheduled and/or repeated measurements will only be included if a scheduled measurement is not available and the unscheduled/repeated measurement falls within the analysis visit windows as described in Table 3. The windows follow the Schedule of Events in Table 1 and Table 2. Unscheduled/repeated measurements will be listed.

Table 3: Analysis Visit Windows

Visit	Target Start Day	Lower Limit	Upper Limit
1		-97	-1
2	1	1	1
3	14	9	19
4	30	23	37
5	60	53	67
6	90	83	97
7	104	99	109
8	120	113	127
9	150	143	157
10	180	173	187
11	194	194	194

Visit windows may be extended (as reasonable) so as to accommodate delays for assessments due to the COVID-19 pandemic.

6.1.6. Pooling of Sites

Not applicable. Site will be 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, an ad hoc analysis by site may be performed.

6.1.7. Derived Variables

- IGA average score = in protocol version 1.0, IGA was assessed by body area (chest/abdomen, back, arms, and legs). Under protocol version 2.0, this was changed to a global (overall) assessment. For comparability, the average of the body area IGA results will be taken to yield one score for subjects enrolled under protocol version 1.0. Scores will range from 0 to 4. Higher scores indicate worse disease.

- VIIS total score = sum of the individual body area scaling scores, with a range of 0 to 16. Each individual item is scored on a scale of 0-4, where 0 = normal skin; no perceptible scale or smoothening and 4 = confluent, primarily large, thick scales. Higher scores indicate worse scaling.

- Ectropion total score = sum of the 8 individual item scores (lateral apposition, medial apposition, scleral show, conjunctival show, excess tear film, redness of the eye, round canthus, punctum lacrimale), with a range of 0 to 8. Each individual item is scored 0

(nonaffected/no/invisible), 0.5 (≤1 mm/emerging), or 1 (affected/yes/visible). Higher scores indicates worse ectropion.

- DLQI total score = sum of the 10 individual item scores, with a range of 0 to 30. Higher scores indicate poorer quality of life.
- CDLQI total score = sum of the 10 individual item scores, with a range of 0 to 30. Higher scores indicate poorer quality of life.
- Number of doses taken = total number of tubes returned – total number of tubes returned unused
- Number of weeks on study = (last day on study – treatment start date + 1) / 7
- Number of expected doses = 2 * number of weeks on study
- Total weight used = total weight of tubes dispensed (grams) – total weight of tubes returned (grams)
- Initial application amount used = tube weight before drug application (grams) – tube weight after drug application (grams), as collected on the initial study drug application CRF
- Compliance by tube weight = total weight used / total weight of tubes dispensed *100%
- Compliance by number of doses = number of doses taken / number of expected doses * 100%
- Change from baseline = value at current time point – value at baseline.
- TEAE = An AE is defined as treatment emergent if the onset or worsening is at the time of or following the start of the first application of study drug (trifarotene or vehicle) through the Follow-up Visit or Early Termination Visit, whichever occurs first..

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in 4 decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events will be coded using the MedDRA version 21.1 thesaurus. Concomitant mediations will be coded using the WHO-DD version September 2018.

A treatment-related AE is any AE with a relationship to the study drug of possibly related and related.

If partial AE or medication dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows:

For partial AE and medication start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of first dose date and the end date (if present) is after first dose date, then impute as the month and day of the first dose date.
    - Otherwise, assign 01 January.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the first dose date, then impute as the day of the first dose date.
    - Otherwise, assign 01.

For partial AE and medication end dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of the last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination otherwise), then impute as the month and day of the last date of the study.
    - Otherwise, assign 31 December.
- If the year and month are known, but the day is unknown, then:
    - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.
    - Otherwise, assign the last day of the month.

If partial times occur, the convention is as follows:

- if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00;
- if the date is the same as the date of the first dose and

- only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later;
- only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later;

- Otherwise if the date is not the same as the date of first dose, the hour assigned is 12 if the hour is missing and the minute assigned is 30 if the minute is missing.

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

Disposition will include tabulations of the number of subjects randomized into each treatment group, the number of subjects completing Day 90 of the study, the number of subjects withdrawing early from the Double-blind Period, tabulated reasons for withdrawal from the Double-blind Period, and number of subjects in each analysis population. This analysis will be conducted on the ITT population.

Additionally, the number of subjects entering the OLE, completing the study through OLE follow up (Day 194), withdrawing early from the OLE, and tabulated reasons for withdrawal from the OLE will be presented for the OLE ITT population.

If a subject discontinues due to COVID-19, those reasons will also be presented.

7.2. Protocol Violations and Deviations

Major protocol violations, including those due to the impact of COVID-19, as determined by a Sponsor blinded review of the data prior to database lock and unblinding of the study, may result in the removal of a subject's data from the PP population.

All protocol violations will be presented in a data listing, with a flag to indicate if a violation was considered major and resulted in the exclusion of the subject from the PP population.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, height, weight, BMI, and baseline IGA score will be presented by treatment group. See Section 6.1.1 for definition of baseline.

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

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class (SOC) and preferred term (PT), will be tabulated by treatment group. This analysis will be conducted for the Safety population.

Prior medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using WHO-DDE ATC Class Level 4 and preferred term (ATC Class Level 5) and will be presented by treatment group and overall. This analysis will be conducted for the Safety population. Prior medications are defined in Section 9.7.

7.4. Exposure and Compliance

Compliance by tube weight and compliance by number of doses will be summarized by treatment group using descriptive statistics. The total weight of tubes dispensed and returned, as well as total number of tubes dispensed, returned, and returned unused will also be summarized. This analysis will be conducted for the Safety population and for the OLE Safety population.

A subject is compliant with study product if he or she takes at least 80%-120% of the scheduled doses as assessed by number of doses taken reported, supplemented by tube weight and diary entries. The number and percentage of subjects who were compliant will be tabulated by treatment group for the Double-blind Period and overall for the OLE. Derivations of compliance are defined in Section 6.1.7.

All initial study drug application, drug accountability (dispensed and returned), and subject diary data collected will be listed. Changes in treatment administration or treatment dispensation due to COVID-19 including start and end dates of change, method of alternative administration/dispensation, dosing interruptions, and relevant changes to compliance expectations (weights or tube counts) will be documented from the COVID-19 visit impact log.

8. Efficacy Analysis

All efficacy endpoints will be summarized using the ITT population. The primary analysis will be repeated in the mITT and PP populations.

Summaries of efficacy variables in the OLE will be provided using the OLE ITT. Primary IGA summaries will also be provided for the OLE mITT and OLE PP populations. For continuous efficacy analyses using MMRM, only formal comparisons of change from baseline will be performed in the OLE. No other formal inferential analyses will be conducted for efficacy variables in the OLE.

All efficacy data, regardless of population, will be presented in data listings.

If alternative methods are used for capturing efficacy assessments (i.e., in person not on site at the subject's home, remotely with visual aid, or remotely via telephone), additional sensitivity or subgroup analyses may be performed to assess the potential impact to efficacy analyses. These will be delineated as ad hoc analyses in the CSR.

8.1. Primary Efficacy Analysis

8.1.1. Investigator's Global Assessment (IGA)

The 5-point IGA is a measure of disease severity and meets the need for a clinically meaningful measure of success for ichthyosis studies. Each level of severity will consider both the severity of scaling and the severity of roughness. The investigator will rate the subject's condition using the 5-point scale (0-4), excluding the following areas: knees, elbows, neck, palms, soles, axillae, groin, and scalp, where higher scores represent more severe disease. The IGA is collected at all clinic visits. The scoring is as follows below in Table 4.

Table 4: IGA Scoring Definitions

Score	Definition
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 (>1cm) thick scales with plate-like hyperkeratosis

The primary efficacy endpoint is 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. The number and percentage of subjects with treatment success will be summarized by treatment group. The primary efficacy endpoint will be analyzed using a logistic regression model with treatment, baseline IGA score, and age group as factors. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HEI groups and vehicle cream group, 95% CIs for the differences, and *P* values for the differences in treatment will also be presented.

The potential for heterogeneity of treatment effects will be assessed by testing treatment-by-factor interactions. The logistic regression model for the primary analyses will be expanded to include the treatment-by-age group interaction. In the event of quasi or complete separation, the logistic regression model will use Firth's penalized maximum likelihood estimation.

The same logistic regression model will be used to analyze the proportion of subjects with at least a 50% reduction in IGA score from baseline as a secondary analysis.

The change from baseline IGA score will be analyzed using a mixed model for repeated measures (MMRM). The MMRM model will include change from baseline in IGA score as the dependent variable, treatment, study visit, treatment-by-visit interaction, and age group as fixed effects, subject as a random effect, and baseline IGA score as a covariate. All post-baseline study visits will be included in the model; however, the primary comparison will be between the active trifarotene cream HE1 groups and vehicle at Day 90. An unstructured covariance matrix will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate degrees of freedom. In case of convergence issues, other covariance structures will be explored including autoregressive (AR(1)), compound symmetry (CS), and variance components (VC) with each model fit to find the covariance structure with the best fit. The fit statistics will be compared for all covariance structures; the structure with the smallest Akaike information criterion will be retained as the preferred model and noted in the resulting table. For the OLE period, the model will not include treatment or treatment-by-visit interaction since all subjects receive the same treatment in the OLE.

The least squares (LS) mean change from baseline will be presented along with the associated 95% CI within each treatment group. The overall *P* value of the model will be presented to test

the null hypothesis that the change from baseline to subsequent study visit is 0 with a 2-sided alternative considering a difference in either direction.

In comparing treatments (active trifarotene cream HE1 groups minus vehicle), LS mean differences in change from baseline will be presented along with associated 95% CIs and *P* values. The null hypothesis that the difference in change from baseline in active trifarotene cream HE1 groups minus control vehicle is 0 with a 2-sided alternative considering a difference in either direction. Even if a difference from vehicle is observed, as described above, successful treatment is defined as clear/almost clear overall (IGA scores of 0 or 1) and at least a 2-grade change from baseline.

The observed value and change from baseline in IGA score will also be summarized descriptively by study visit and treatment group using descriptive statistics in addition to the above noted models for the Double-blind Period and OLE. Categorical IGA scores will also be presented.

8.1.2. Multiple Imputation

Multiple imputation (MI) of the primary endpoint will be performed as an analysis of sensitivity to missing data in the Double-blind Period only. Following database lock, thorough assessment on the extent of missing data due to COVID-19 will be carried out specifically as pertains to the primary and secondary endpoints. This will inform decisions around reasonability of imputing missing data for secondary endpoints in the Double-blind Period as well. The final determination will be documented in the CSR.

MI assumes that the statistical behavior of drug- and control-treated subjects after discontinuing study drug becomes that of the vehicle group. Multiple-imputations will be used to replace missing IGA outcomes using multiple draws from the posterior predictive distribution estimated from the vehicle treatment group. IGA scores will be imputed and then categorized as treatment success according to Section 8.1.1 above. A placebo-based pattern mixture model (PMM) will be utilized following the steps outlined in Ratitch B and O'Kelly, M.J. (2011)[4].

Data are processed sequentially by repeatedly calling SAS® PROC MI to impute missing outcomes at study visit t = 1, …, T. The following procedure is followed:

- *Initialization (Step 1)*. Set t = 0 (baseline study visit).
- *Iteration (Step 2)*. Set t = t + 1. Create a dataset combined records from drug- and vehicle-treated subjects with columns for covariates **X** and outcomes at study visits 1, …, t with outcomes for all subjects set to missing at study visit t and set to observed or imputed values at study visits 1, …, t-1.
- *Imputation (Step 3)*. Run placebo-based pattern mixture model in SAS® PROC MI on this data to impute missing values for study visit *t* using previous outcomes for study visit 1 to t-1 and baseline covariates.
    - Replace imputed data for all subjects at study visit t with their observed values, whenever available. If t < T then go to Step 2, otherwise proceed to Step 4.
    - Repeat steps 1-3, *m* times with different seed values to create *m* imputed complete datasets. In this analysis, *m* will be assigned 50.

- *Analysis (Step 4)*. For each completed dataset use the model as it would have been applied had the data been complete for the continuous outcome. The final inference on treatment difference is conducted from the multiple datasets, as implemented in SAS® PROC MI ANALYZE.

The steps for this approach are detailed below:

1. Transpose data horizontally by study visit and impute all non-monotone (intermittent) missing data using the Markov Chain Monte Carlo (MCMC) method of PROC MI. Note that this imputation will sample data within each treatment group. SAS pseudo code is provided below.

```
PROC MI DATA=example seed = 6654 NIMPUTE = 20 OUT = outdata1;
       BY <treatment>;
       MCMC chain=multiple impute=monotone;
       VAR <treatment> <baseline score>  <visitX score> .. <visit6 score>;
RUN;
```

2. Using the imputed datasets from Step #1 that are now monotone missing (no intermittent missing data), a single call to PROC MI (including the MNAR statement) will be utilized to impute the monotone missing data. Within the call to PROC MI, one timepoint is imputed at a time. When imputing at time-point *t*, the imputation step will include all vehicle subjects, but only those from the active arms that have a value missing at time-point *t*. Subjects with non-missing data that are on active arms will not contribute to the estimation for this step.

Repeat the above step for all timepoints *t*. Thus, the data for timepoint t+1 uses the data imputed from previous timepoints.

SAS pseudo code is provided below. SAS accomplishes this iterative process in one step.

```
PROC MI DATA=example seed = 2617 NIMPUTE = 1 OUT = outdata1;
       BY  _imputation_;
       CLASS <treatment>;
       MONOTONE REG ( / details);
       MNAR MODEL (<v1 score> .. <v6 score> /
              modelobs=(treatment=("vehicle")));
       VAR <baseline score> <v1 score> .. <vX score>..<v6 score> ;
RUN;
```

3. Pass the output from Step 2 into the model by the imputation variable (coalesce into one from each step above). When all missing data are imputed, PROC MIANALYZE will be used to combine the parameters from the analyses for inference.

8.2. Secondary Efficacy Analyses

8.2.1. Visual Index for Ichthyosis Severity (VIIS)

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 all clinic visits. The scoring is as follows in Table 5.

Table 5: VIIS Scoring Definitions

Score	Definition
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 (visible separated/fractured stratum corneum)
2	Confluent smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visible separated/fractured stratum corneum)
3	Confluent scales (visibly separated/fractured stratum corneum) including some large (>1cm), thick scales
4	Confluent, primarily large, thick scales

The change from baseline VIIS score will be analyzed using an MMRM. The MMRM model will include change from baseline in VIIS score as the dependent variable, treatment, study visit, treatment-by-visit interaction, and age group as fixed effects, subject as a random effect, and baseline VIIS score as a covariate. All post-baseline study visits will be included in the model; however, the primary comparison will be between the active trifarotene cream HE1 groups and vehicle at Day 90. An unstructured covariance matrix will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate degrees of freedom. In case of convergence issues, other covariance structures will be explored including AR(1), CS, and VC with each model fit to find the covariance structure with the best fit. The fit statistics will be compared for all covariance structures; the structure with the smallest Akaike information criterion will be retained as the preferred model and noted in the resulting table. For the OLE period, the model will not include treatment or treatment-by-visit interaction since all subjects receive the same treatment in the OLE.

The LS mean change from baseline will be presented along with the associated 95% CI within each treatment group. The overall *P* value of the model will be presented to test the null hypothesis that the change from baseline to subsequent study visit is 0 with a 2-sided alternative considering a difference in either direction.

In comparing treatments (active trifarotene cream HE1 groups minus vehicle), LS mean differences in change from baseline will be presented along with associated 95% CIs and *P* values. The null hypothesis that the difference in change from baseline in active trifarotene cream HE1 groups minus control vehicle is 0 with a 2-sided alternative considering a difference in either direction.

The observed value and change from baseline in VIIS score will also be summarized descriptively by study visit and treatment group using descriptive statistics in addition to the above noted model for the Double-blind Period and OLE.

8.2.2. Individual Score for Roughness

The amount of roughness of the skin overall will be measured on a 5-point scale at all clinic visits. The scoring is as follows in Table 6.

Table 6: Roughness Scoring Definitions

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

The change from baseline individual score for roughness will be analyzed using an MMRM. The MMRM model will include change from baseline in individual score for roughness as the dependent variable, treatment, study visit, treatment-by-visit interaction, and age group as fixed effects, subject as a random effect, and baseline individual score for roughness as a covariate. All post-baseline study visits will be included in the model; however, the primary comparison will be between the active trifarotene cream HE1 groups and vehicle at Day 90. An unstructured covariance matrix will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate degrees of freedom. In case of convergence issues, other covariance structures will be explored including AR(1), CS, and VC with each model fit to find the covariance structure with the best fit. The fit statistics will be compared for all covariance structures; the structure with the smallest Akaike information criterion will be retained as the preferred model and noted in the resulting table. For the OLE period, the model will not include treatment or treatment-by-visit interaction since all subjects receive the same treatment in the OLE.

The LS mean change from baseline will be presented along with the associated 95% CI within each treatment group. The overall *P* value of the model will be presented to test the null hypothesis that the change from baseline to subsequent study visit is 0 with a 2-sided alternative considering a difference in either direction.

In comparing treatments (active trifarotene cream HE1 groups minus vehicle), LS mean differences in change from baseline will be presented along with associated 95% CIs and *P* values. The null hypothesis that the difference in change from baseline in active trifarotene cream HE1 groups minus control vehicle is 0 with a 2-sided alternative considering a difference in either direction.

The observed value and change from baseline in individual score for roughness will also be summarized descriptively by study visit and treatment group using descriptive statistics in addition to the above noted model for the Double-blind Period and OLE.

Additionally, the proportion of subjects who experience a 2-grade change from baseline to Day 90 in individual score for roughness will be summarized by treatment group and analyzed using a logistic regression model with treatment, baseline individual score for roughness, and age group as factors. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HE1 groups and vehicle cream group, 95% CIs for the differences, and *P* values for the differences in treatment will also be presented.

The potential for heterogeneity of treatment effects will be assessed by testing treatment-by-factor interactions. The logistic regression model for the analysis will be expanded to include the treatment-by-age group interaction. In the event of quasi or complete separation, the logistic regression model will use Firth's penalized maximum likelihood estimation.

8.2.3. Palm/Sole Assessment

Thickening of the skin on the palms and soles will be measured on a 5-point scale at all clinic visits. The scoring is as follows in Table 7.

Table 7: Palm/Sole Scoring Definitions

Score	Definition
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

The change from baseline palm/sole assessment score will be analyzed using an MMRM. The MMRM model will include change from baseline in palm/sole assessment score as the dependent variable, treatment, study visit, treatment-by-visit interaction, and age group as fixed effects, subject as a random effect, and baseline palm/sole assessment score as a covariate. All post-baseline study visits will be included in the model; however, the primary comparison will be between the active trifarotene cream HE1 groups and vehicle at Day 90. An unstructured covariance matrix will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate degrees of freedom. In case of convergence issues, other covariance structures will be explored including AR(1), CS, and VC with each model fit to find the covariance structure with the best fit. The fit statistics will be compared for all covariance structures; the structure with the smallest Akaike information criterion will be retained as the preferred model and noted in the resulting table. For the OLE period, the model will not include treatment or treatment-by-visit interaction since all subjects receive the same treatment in the OLE.

The LS mean change from baseline will be presented along with the associated 95% CI within each treatment group. The overall *P* value of the model will be presented to test the null hypothesis that the change from baseline to subsequent study visit is 0 with a 2-sided alternative considering a difference in either direction.

In comparing treatments (active trifarotene cream HE1 groups minus vehicle), LS mean differences in change from baseline will be presented along with associated 95% CIs and *P* values. The null hypothesis that the difference in change from baseline in active trifarotene cream HE1 groups minus control vehicle is 0 with a 2-sided alternative considering a difference in either direction.

The observed value and change from baseline in palm/sole assessment score will also be summarized descriptively by study visit and treatment group using descriptive statistics in addition to the above noted model for the Double-blind Period and OLE.

Additionally, the proportion of subjects who experience a 2-grade change from baseline to Day 90 in palm/sole assessment score will be summarized by treatment group and analyzed using a logistic regression model with treatment, baseline palm/sole assessment score, and age group as factors. The odds ratios and 95% CIs for the odds ratios will be presented. The difference in proportions between the active trifarotene cream HE1 groups and vehicle cream group, 95% CIs for the differences, and *P* values for the differences in treatment will also be presented.

The potential for heterogeneity of treatment effects will be assessed by testing treatment-by-factor interactions. The logistic regression model for the analysis will be expanded to include the treatment-by-age group interaction. In the event of quasi or complete separation, the logistic regression model will use Firth's penalized maximum likelihood estimation.

8.2.4. Quality of life per Dermatology Life Quality Index (DLQI) and Children's DLQI (cDLQI)

The DLQI is a dermatology-specific Quality of Life instrument for subjects aged 17 years and older. The cDLQI is for subjects aged 12 to 16 years. It is a 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 investigator will use his or her judgment of the maturity of the subject to decide which version of the questionnaire to use; the same version will be used for the subject throughout the study.

The change from baseline DLQI/cDLQI score will be analyzed using an MMRM. The MMRM model will include change from baseline in DLQI/cDLQI score as the dependent variable, treatment, study visit, and treatment-by-visit interactionas fixed effects, subject as a random effect, and baseline DLQI/cDLQI score as a covariate. All post-baseline study visits will be included in the model; however, the primary comparison will be between the active trifarotene cream HE1 groups and vehicle at Day 90. An unstructured covariance matrix will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate degrees of freedom. In case of convergence issues, other covariance structures will be explored including AR(1), CS, and VC with each model fit to find the covariance structure with the best fit. The fit statistics will be compared for all covariance structures; the structure with the smallest Akaike information criterion will be retained as the preferred model and noted in the resulting table.

The LS mean change from baseline will be presented along with the associated 95% CI within each treatment group. The overall *P* value of the model will be presented to test the null hypothesis that the change from baseline to subsequent study visit is 0 with a 2-sided alternative considering a difference in either direction.

In comparing treatments (active trifarotene cream HE1 groups minus vehicle), LS mean differences in change from baseline will be presented along with associated 95% CIs and *P* values. The null hypothesis that the difference in change from baseline in active trifarotene cream HE1 groups minus control vehicle is 0 with a 2-sided alternative considering a difference in either direction.

The observed value and change from baseline in DLQI/cDLQI score will also be summarized descriptively by study visit and treatment group using descriptive statistics in addition to the above noted model for the Double-blind Period.

8.2.5. Fissures

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).

The number and proportion of subjects with fissures present on palms or soles along with 95% CIs will be summarized by treatment group and study visit. A 2-sided Pearson's Chi-Square Test, or Fisher's Exact Test, as appropriate, will be performed at the 5% significance level to determine whether there is a significant difference between treatment groups. The null hypothesis that there is no difference in proportion of subjects with fissures present between active trifarotene cream HE1 and vehicle, with a 2-sided alternative considering a difference in either direction. The difference in proportions between active trifarotene cream HE1 and vehicle (active trifarotene cream HE1 minus vehicle), 95% CIs for the differences, and *P* values for the differences in treatment will also be presented.

The number of fissures and fissure pain level will be summarized descriptively by body area and treatment group.

8.3. Exploratory Efficacy Analyses

8.3.1. Ectropion

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. The scoring is as follows in Table 8.

Table 8: Ectropion Scoring

	Points per Item

	0	0.5	1
Lateral apposition	Nonaffected	-	Affected
Medial apposition	Nonaffected	-	Affected
Sceral show	No	≤ 1 mm	> 1mm
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

The observed value and change from baseline in ectropion score will be summarized descriptively by study visit and treatment group using descriptive statistics for the Double-blind Period and OLE.

8.3.2. Quality of Life per EQ-5D-5L and EQ-5D-Y

The EQ-5D is a measure of health related quality of life. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS). The EQ-5D-5L is intended for use in adult subjects, while the EQ-5D-Y is to be used for children and adolescents. The investigator will use his or her judgment of the maturity of the subject to decide which version of the EQ-5D to use; the same version will 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.

The observed value and change from baseline in EQ-5D-5L/EQ-5D-Y score will be summarized descriptively by study visit and treatment group using descriptive statistics for the Double-blind Period and OLE.

9. Safety and Tolerability Analysis

Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, local tolerability assessments, and physical examination results. No formal inferential analyses will be conducted for safety variables in either period.

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.

9.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary Version 21.1.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with study drug through 14 days after the last application of study drug, 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 study drug through the last application of study drug.

The causal relationship of the AE to the study drug is determined by the investigator as Not Related, Unlikely Related, Possibly Related, and Related. These will be mapped to Unrelated (Not Related or Unlikely Related) and Related (Possibly Related, or Related).

Adverse event severity grades are reported as mild, moderate, or severe.

Summaries of incidence rates (frequencies and percentages) of individual TEAEs will be presented by SOC, PT, and treatment group for the Double-blind Period and OLE. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity, and TEAEs by relationship.

Each subject will be counted only once within each summation level (SOC and PT). If a subject experiences more than 1 TEAE within each summation level, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = related).

Incidences will be presented by descending frequency of SOC and PT within SOC, and then alphabetically within PT where the incidence is the same; this is based on overall subjects then alphabetically in case of a tie.

Missing and partially missing AE start and/or stop dates and times will be imputed, for the purpose of statistical analysis, according to the specifications described in Section 6.1.8.

In the AE data listings, all AEs will be displayed. AEs that are treatment emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and PT will be prepared for both the Double-blind Period and OLE.

A data listing of AEs leading to withdrawal of study drug during each period will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by SOC and PT and presented by treatment group for the Double-blind Period and overall for the OLE.

9.2. Clinical Laboratory Evaluations

Laboratory tests (clinical chemistry, hematology, coagulation, and quantitative urinalysis) will be performed at Screening, Baseline, Day 30, Day 90, Day 120, and Day 180. Results will be summarized descriptively by treatment group and study visit as both observed values and change from baseline values for the Double-blind Period and OLE. See Section 6.1.1 for the definition of baseline. Number and percentage of subjects with abnormal qualitative urinalysis results will be provided by treatment group and study visit.

The number of subjects with clinical laboratory values below, within, or above normal ranges, by study visit will be tabulated (shift tables) for each clinical laboratory parameter by treatment group.

Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged and presented along with corresponding normal ranges (if available). A separate listing of abnormal laboratory values will be provided. All study visits within a parameter for a subject will be presented if at least 1 study visit within that parameter has an abnormal result.

Serology results and pregnancy test results will be listed separately.

9.3. Vital Signs

Vital signs will be collected at Screening, Baseline, Day 14, Day 30, Day 60, Day 90, Day 120, Day 150, Day 180, and Day 194. Descriptive summaries of actual values and changes from baseline will be calculated for systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and pulse (bpm).

The number of subjects with vital sign values below, within, or above normal ranges, by study visit will be tabulated (shift tables) for each parameter by treatment group.

These summaries will be presented by study visit and treatment group. See Section 6.1.1 for the definition of baseline.

9.4. Electrocardiograms

12-Lead ECGs will be collected at Screening, Baseline, Day 30, Day 90, Day 120, and Day 180. For subjects in the PK substudy, additional ECGs will be performed postdose during serial blood sampling on Day 1 and Day 30. Descriptive summaries will be presented for heart rate (bpm),

PR interval (ms), QRS interval (ms), uncorrected QT interval (ms), QTcF (ms). These summaries will be presented by study visit and treatment group.

The number and percentage of subjects with normal and abnormal ECG results will be summarized by treatment group and study visit.

9.5. 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 of the investigator's assessment of erythema, stinging/burning, and pruritus will be presented by body area, period, treatment group, and study visit.

9.6. Physical Examination

Physical examinations will be performed at Screening, Baseline, Day 90, Day 180, and Day 194. 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.

9.7. Concomitant Medication

Prior and concomitant medications, coded using World Health Organization-Drug Dictionary Enhanced (WHO-DDE) (September 2018), will be summarized descriptively by Anatomical Therapeutic Chemical (ATC) classification Level 4 and PT (i.e., ATC classification Level 5), if applicable, using counts and percentages for the Safety Population.

Prior medications and concomitant medications will be presented separately. The assignment of medications as prior and/or concomitant will be done as follows:

- **Prior medications:** Medications that started before the first dose of study drug will be considered prior medications whether or not they were stopped before dose.
- **Concomitant medications:** Any medications continuing or starting after the first dose of study drug through the end of study will be considered to be concomitant.

If a medication starts prior to the first dose and continues after the first dose it will be considered both prior and concomitant. Prior and concomitant medications will also be listed. Prior and concomitant medications will be summarized descriptively by treatment using counts and percentages.

9.8. COVID-19 Visit Impact

A listing of the COVID-19 visit impact log will be presented which will display which (if any) study visits were impacted by the pandemic. The listing will display if the visit was performed and if the visit type was adjusted as well as ths reason(s) for adjustment.

10. Changes from Planned Analysis

Age was added as a factor for MMRM analyses because the study is enrolling both adults and

adolescents.

11. Other Planned Analysis

11.1. Pharmacokinetic Analysis

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

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 plasma concentration-time curve from time 0 to the time of the last quantifiable plasma concentration (AUC_{0-t}), Area under the plasma concentration-time curve from time 0 to infinity (if data permits) (AUC_{0-inf}) and rate-of-absorption using the maximum serum concentration (C_{max}), the time of C_{max} (T_{max}), apparent first order terminal elimination half-life ($t_{1/2}$), apparent terminal phase rate constant (λ_z) (if data permits).

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.

11.2. Photography

Photography collection dates will be listed.

12. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.
4. Ratitich, B. and O'Kelly, M.J. (2011). Implementation of Pattern-Mixture Models Using Standard SAS / STAT Procedures.

13. Tables, Listings, and Figures

All listings, tables, and figures will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize the presentation with common notations.

General Reporting Conventions

- All tables and data listings will be developed in landscape orientation.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as nonprintable control characters, printer-specific characters, or font specific characters, will not be used on a table, figure, or data listing.
- All titles will be centered on a page. All footnotes will be left justified and at the bottom of a page.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A value of zero may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as ddmmmyyyy (e.g., 29AUG2011) format.
- If applicable, all observed time values will be presented by using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
- Adverse events with missing MedDRA coding will have their system organ class and/or

preferred term presented as "Not Coded" in the tables. The "Not Coded" frequencies will be sorted to the end of the tables. This will only be applicable for any deliveries sent before database lock (e.g., for dry runs on blinded data).

- Programming notes may be inserted into the shells, these notes will not appear in the final output.

Population Summary Conventions

- Population sizes may be presented for each classification factor as totals in the column header as (N=xxx), where appropriate.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed; however, counts and percentages of missing values may be needed.
- All population summaries for continuous variables will include: N, mean, SD, median, minimum, and maximum. Other summaries (e.g., number missing, 95% CIs) may be used as appropriate. The precision of the maximum and minimum will match the maximum precision in the data. The mean and median will have 1 additional decimal place. The SD will have 2 additional decimal places.
- All percentages are rounded (where, for example, 0.05% is rounded up to 0.1%) and reported to a single decimal point (xx.x%).
- A percentage of 0% will not be displayed (i.e., only the count of 0 will be displayed), and a percentage of 100% will be displayed with 0 decimal places.
- All *P* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

13.1. Planned Table Descriptions

The following are planned summary tables for protocol number 18-ICH-001. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Table 9: Demographic Data Summary Tables and Figures

Number	Population	Title	Unique/Non-unique
Table 14.1.1.1	ITT	Summary of Subject Disposition	Unique
Table 14.1.1.2	OLE ITT	Summary of Subject Disposition	Non-unique
Table 14.1.2.1	ITT	Demographics and Baseline Characteristics	Unique
Table 14.1.2.2	OLE ITT	Demographics and Baseline Characteristics	Non-unique
Table 14.1.3	Safety	Summary of Medical Histories by System Organ Class and Preferred Term	Unique
Table 14.1.4	Safety	Summary of Prior Medications by ATC Class Level 4 and Preferred Term	Unique
Table 14.1.5.1	Safety	Summary of Drug Accountability (Drug Returned and Dispensed)	Unique
Table 14.1.5.2	OLE Safety	Summary of Drug Accountability (Drug Returned and Dispensed)	Non-unique
Table 14.1.5.3	Safety	Summary of Treatment Exposure and Compliance	Unique
Table 14.1.5.4	OLE Safety	Summary of Treatment Exposure and Compliance	Non-unique

13.2. Efficacy Data

Table 10: Efficacy Data

Number	Population	Title	Unique/Non-unique
14.2.1.1.1	ITT	Primary Analysis: Logistic Regression Analysis of Successful Resolution of LI	Unique
14.2.1.1.2	OLE ITT	Proportion of Subjects with Successful Resolution of LI in the OLE	Unique
14.2.1.2.1	mITT	Primary Analysis, Sensitivity: Logistic Regression Analysis of Successful Resolution of LI	Non-unique
14.2.1.2.2	OLE mITT	Proportion of Subjects with Successful Resolution of LI in the OLE	Non-unique
14.2.1.3.1	PP	Primary Analysis, Sensitivity: Logistic Regression Analysis of Successful Resolution of LI	Non-unique

Number	Population	Title	Unique/Non-unique
14.2.1.3.2	OLE PP	Proportion of Subjects with Successful Resolution of LI in the OLE	Non-unique
14.2.1.4	ITT	Primary Analysis, Sensitivity: Logistic Regression Analysis of Successful Resolution of LI Using Multiple Imputation	Non-unique
14.2.1.5.1	ITT	Logistic Regression Analysis of 50% Reduction in IGA score from Baseline	Non-unique
14.2.1.5.2	OLE ITT	Proportion of Subjects with a 50% Reduction in IGA score from Baseline	Non-unique
14.2.1.6.1	ITT	MMRM Analysis of Change from Baseline in IGA Score	Unique
14.2.1.6.2	OLE ITT	MMRM Analysis of Change from Baseline in IGA Score	Non-unique
14.2.1.7.1	ITT	Categorical IGA Scores	Unique
14.2.1.7.2	OLE ITT	Categorical IGA Scores	Non-unique
14.2.2.1	ITT	Secondary Analysis: MMRM Analysis of Change from Baseline in VIIS Score	Non-unique
14.2.2.2	OLE ITT	MMRM Analysis of Change from Baseline in VIIS Score	Non-unique
14.2.3.1	ITT	Secondary Analysis: MMRM Analysis of Change from Baseline in Individual Score for Roughness	Non-unique
14.2.3.2	OLE ITT	MMRM Analysis of Change from Baseline in Individual Score for Roughness	Non-unique
14.2.3.3	ITT	Logistic Regression Analysis of 2-grade Change in Individual Score for Roughness from Baseline	Non-unique
14.2.4.1	ITT	Secondary Analysis: MMRM Analysis of Change from Baseline in Palm/Sole Assessment	Non-unique
14.2.4.2	OLE ITT	MMRM Analysis of Change from Baseline in Palm/Sole Assessment	Non-unique
14.2.4.3	ITT	Logistic Regression Analysis of 2-grade Change in Palm/Sole Assessment from Baseline	Non-unique
14.2.5.1	ITT	Secondary Analysis: MMRM Analysis of Change from Baseline in Dermatology Life Quality Index	Non-unique
14.2.5.2	ITT	Secondary Analysis: MMRM Analysis of Change from Baseline in Children's Dermatology Life Quality Index	Non-unique
14.2.6.1.1	ITT	Secondary Analysis: Presence of Fissures on Palms or Soles	Unique
14.2.6.1.2	OLE ITT	Presence of Fissures on Palms or Soles	Unique
14.2.6.2.1	ITT	Secondary Analysis: Summary of Number of Fissures and Fissure Pain Level	Unique
14.2.6.2.2	OLE	Summary of Number of Fissures and Fissure Pain Level	Non-unique

Number	Population	Title	Unique/Non-unique
14.2.7.1	ITT	Exploratory Analysis: Summary of Change from Baseline in Ectropion Score	Unique
14.2.7.2	OLEITT	Summary of Change from Baseline in Ectropion Score	Non-unique
14.2.8.1	ITT	Exploratory Analysis: Change from Baseline in EQ-5D-5L	Non-unique
14.2.8.2	ITT	Exploratory Analysis: Change from Baseline in EQ-5D-Y	Non-unique

13.3. Safety Data

Table 11: Safety Data

Number	Population	Title	Unique/Non-unique
14.3.1.1.1	Safety	Overall Summary of Treatment Emergent Adverse Events during the Double-blind Period	Unique
14.3.1.1.2	OLE Safety	Overall Summary of Treatment Emergent Adverse Events during the OLE	Non-unique
14.3.1.2.1	Safety	Incidence of Treatment Emergent Adverse Events during the Double-blind Period by System Organ Class and Preferred Term	Unique
14.3.1.2.2	OLE Safety	Incidence of Treatment Emergent Adverse Events during the OLE Period by System Organ Class and Preferred Term	Non-unique
14.3.1.3.1	Safety	Incidence of Treatment Emergent Adverse Events during the Double-blind Period by System Organ Class, Preferred Term, and Maximum Severity	Unique
14.3.1.3.2	OLE Safety	Incidence of Treatment Emergent Adverse Events during the OLE by System Organ Class, Preferred Term, and Maximum Severity	Non-unique
14.3.1.4.1	Safety	Incidence of Treatment Emergent Adverse Events during the Double-blind Period by System Organ Class, Preferred Term, and Relationship to Study Drug	Unique
14.3.1.4.2	OLE Safety	Incidence of Treatment Emergent Adverse Events during the OLE by System Organ Class, Preferred Term, and Relationship to Study Drug	Non-unique
14.3.2.1.1	Safety	Incidence of Adverse Events Leading to Withdrawal during the Double-blind Period by SOC, PT, and Treatment	Non-unique
14.3.2.1.2	OLE Safety	Incidence of Adverse Events Leading to Withdrawal during the OLE Period by SOC, PT, and Treatment	Non-unique
14.3.2.2.1	Safety	Incidence of Serious Adverse Events during the Double-blind Period by SOC, PT, and Treatment	Non-unique
14.3.2.2.2	OLE Safety	Incidence of Serious Adverse Events during the OLE by SOC, PT, and Treatment	Non-unique
14.3.3.1.1	Safety	Listing of Adverse Events Leading to Withdrawal during the Double-blind Period	Unique
14.3.3.1.2	OLE Safety	Listing of Adverse Events Leading to Withdrawal during the Double-blind Period	Non-unique
14.3.3.2.1	Safety	Listing of Serious Adverse Events during the Double-blind Period	Non-unique
14.3.3.2.2	Safety	Listing of Serious Adverse Events during the OLE	Non-unique
14.3.3.3.1	Safety	Listing of Deaths during the Double-blind Period	Non-unique

Number	Population	Title	Unique/Non-unique
14.3.3.3.2	Safety	Listing of Deaths during the OLE	Non-unique
14.3.4.1	Safety	Listing of Abnormal Laboratory Data	Unique
14.3.5.1.1.1	Safety	Laboratory Data: Change from Baseline in Clinical Chemistry Parameters by Study Visit	Unique
14.3.5.1.1.2	OLE Safety	Laboratory Data: Change from Baseline in Clinical Chemistry Parameters by Study Visit	Non-unique
14.3.5.1.2.1	Safety	Laboratory Data: Shift from Baseline in Clinical Chemistry Parameters by Study Visit	Unique
14.3.5.1.2.2	OLE Safety	Laboratory Data: Shift from Baseline in Clinical Chemistry Parameters by Study Visit	Non-unique
14.3.5.2.1.1	Safety	Laboratory Data: Change from Baseline in Hematology Parameters by Study Visit	Non-unique
14.3.5.2.1.2	OLE Safety	Laboratory Data: Change from Baseline in Hematology Parameters by Study Visit	Non-unique
14.3.5.2.2.1	Safety	Laboratory Data: Shift from Baseline in Hematology Parameters by Study Visit	Non-unique
14.3.5.2.2.2	OLE Safety	Laboratory Data: Shift from Baseline in Hematology Parameters by Study Visit	Non-unique
14.3.5.3.1.1	Safety	Laboratory Data: Change from Baseline in Coagulation Parameters by Study Visit	Non-unique
14.3.5.3.1.2	OLE Safety	Laboratory Data: Change from Baseline in Coagulation Parameters by Study Visit	Non-unique
14.3.5.3.2.1	Safety	Laboratory Data: Shift from Baseline in Coagulation Parameters by Study Visit	Non-unique
14.3.5.3.2.2	OLE Safety	Laboratory Data: Shift from Baseline in Coagulation Parameters by Study Visit	Non-unique
14.3.5.4.1.1	Safety	Laboratory Data: Change from Baseline in Quantitative Urinalysis Parameters by Study Visit	Non-unique
14.3.5.4.1.2	OLE Safety	Laboratory Data: Change from Baseline in Quantitative Urinalysis Parameters by Study Visit	Non-unique
14.3.5.4.2.1	Safety	Laboratory Data: Shift from Baseline in Quantitative Urinalysis Parameters by Study Visit	Non-unique
14.3.5.4.2.2	OLE Safety	Laboratory Data: Shift from Baseline in Quantitative Urinalysis Parameters by Study Visit	Non-unique
14.3.5.4.3.1	Safety	Laboratory Data: Summary of Qualitative Urinalysis Parameters by Study Visit	Unique

Number	Population	Title	Unique/Non-unique
14.3.5.4.3.2	OLE Safety	Laboratory Data: Summary of Qualitative Urinalysis Parameters by Study Visit	Non-unique
14.3.6.1.1	Safety	Summary of Vital Signs by Study Visit	Non-unique
14.3.6.1.2	OLE Safety	Summary of Vital Signs by Study Visit	Non-unique
14.3.6.2.1	Safety	Summary of 12-Lead Electrocardiogram by Study Visit	Non-unique
14.3.6.2.2	OLE Safety	Summary of 12-Lead Electrocardiogram by Study Visit	Non-unique
14.3.6.2.3	Safety	Summary of 12-Lead Electrocardiogram Interpretation by Study Visit	Unique
14.3.6.2.4	OLE Safety	Summary of 12-Lead Electrocardiogram Interpretation by Study Visit	Unique
14.3.6.3.1	Safety	Summary of Local Tolerability Assessments by Study Visit	Unique
14.3.6.3.2	OLE Safety	Summary of Local Tolerability Assessments by Study Visit	Non-unique
14.3.6.4.1	Safety	Summary of Physical Examination Results by Study Visit	Unique
14.3.6.4.2	OLE Safety	Summary of Physical Examination Results by Study Visit	Non-unique
14.3.6.5.1	Safety	Summary of Concomitant Medications by ATC Class Level 4 and Preferred Term	Non-unique
14.3.6.5.2	OLE Safety	Summary of Concomitant Medications by ATC Class Level 4 and Preferred Term	Non-unique

13.4. Pharmacokinetic Data

Table 12: Pharmacokinetic Data

Number	Population	Title	Unique/Non-unique
14.4.1.1	Safety	Summary of Pharmacokinetic Concentrations by Study Visit	Unique
14.4.1.2	Safety	Summary of Pharmacokinetic Parameters	Unique

13.5. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number 18-ICH-001.

In general, 1 listing will be produced per CRF domain. All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for 1 subject will be kept on 1 page if at all possible, rather than splitting a subject's information across pages.

Table 13: Planned Listings

Number	Population	Title	Unique/Non-unique	Provide at Topline?
16.2.1	All Subjects	Subject Disposition	Unique	
16.2.2.1	All Subjects	Inclusion and Exclusion Criteria	Unique	
16.2.2.2	All Subjects	Screen Failures	Unique	
16.2.2.3	All Subjects	Protocol Deviations	Unique	
16.2.3	All Subjects	Analysis Populations	Unique	
16.2.4.1	All Subjects	Subject Demographics	Unique	
16.2.4.2	All Subjects	Informed Consent and Reconsent	Unique	
16.2.4.3	All Subjects	Medical History	Unique	
16.2.5.1	All Subjects	Initial Study Drug Application	Unique	
16.2.5.2	All Subjects	Drug Accountability (Dispensed and Returned)	Unique	
16.2.5.3	All Subjects	Subject Diary	Unique	
16.2.5.4.1	All Subjects	Pharmacokinetic Sample Collection	Unique	
16.2.5.4.2	All Subjects	Pharmacokinetic Sample Collection (Substudy)	Unique	
16.2.5.4.3	PK	Pharmacokinetic Concentrations	Unique	

Number	Population	Title	Unique/Non-unique	Provide at Topline?
16.2.5.4.4	All Subjects	Pharmacokinetic Calculated Parameters	Unique	
16.2.6.1	All Subjects	Investigator's Global Assessment (IGA)	Unique	
16.2.6.2	All Subjects	Visual Index for Ichthyosis (VIIS)	Non-unique	
16.2.6.3	All Subjects	Roughness Assessment	Non-unique	
16.2.6.4	All Subjects	Palm/Sole Assessment	Non-unique	
16.2.6.5.1	All Subjects	Quality of Life per Dermatology Life Quality Index (DLQI)	Non-unique	
16.2.6.5.1	All Subjects	Quality of Life per Children's Dermatology Life Quality Index (DLQI)	Non-unique	
16.2.6.6	All Subjects	Fissuring Assessment	Unique	
16.2.6.7	All Subjects	Ectropion Score	Non-unique	
16.2.6.8	All Subjects	EQ-5D	Non-unique	
16.2.7.1	All Subjects	Adverse Events	Unique	
16.2.8.1	All Subjects	Laboratory Data: Clinical Chemistry	Unique	
16.2.8.2	All Subjects	Laboratory Data: Hematology	Non-unique	
16.2.8.3	All Subjects	Laboratory Data: Coagulation	Non-unique	
16.2.8.4	All Subjects	Laboratory Data: Urinalysis	Non-unique	
16.2.8.5	All Subjects	Laboratory Data: Serology	Non-unique	
16.2.8.6	All Subjects	Laboratory Data: Pregnancy Tests	Non-unique	
16.2.9.1	All Subjects	Vital Signs	Non-unique	
16.2.9.2	All Subjects	12-Lead Electrocardiogram	Non-unique	
16.2.9.3	All Subjects	Local Tolerability Assessments	Unique	
16.2.9.4	All Subjects	Physical Examination	Unique	
16.2.9.5	All Subjects	Prior and Concomitant Medications	Unique	
16.2.9.6	All Subjects	Photography	Unique	
16.2.9.7	All Subjects	Trial Continuation	Unique	
16.2.9.8	All Subjects	Telephone Contact	Unique	
16.2.9.9	All Subjects	COVID-19 Visit Impact Log	Unique	

13.6. Planned Figure Descriptions

Not applicable.

Table 14: Planned Figures

Not Applicable.

14. Tables, Listings, and Listing Shells

14.1. Standard Layout for all Tables, Listings, and Figures

The following standard layout will be applied to all tables, listings, and figures in support of this study. Note that programming notes may be added if appropriate after each TLF shell.

Figure 3: Standardized Layout

Mayne Pharma — Page xx of xx

Protocol: 18-ICH-001 — <Version>

<Table, Listing, Figure> xx.x.x

<Title of Table Listing or Figure>

<Study Population and if applicable subgroup Description>

Body of Table, Listing or Figure

<Note: If directly Applicable>

Footnote 1 *<if applicable>* Recommendation is to keep footnotes to a minimum

Footnote 2 *<if applicable>*

Footnote n *<if applicable>*

<pgm path>\<pgm name.sas>

Executed on DDMONYYYY at hh:mm on data from DDMONYYYY; SAS Version 9.X

14.2. Planned Table Shells

See Figure 4 below.

Figure 4: Planned Table Shells

Table 14.1.1.1
Summary of Subject Disposition
ITT Population

Category	Trifarotene cream HE1 100 ug/g (N=XXX)	Trifarotene cream HE1 200 ug/g (N=XXX)	Vehicle (N=XXX)	Overall (N=XXX)
ITT Population	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Safety Population	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
mITT Population	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
PP Population	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
PK Population	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Completed Continuing	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Completed not Continuing to OLE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ongoing in Double-blind Study	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Early Discontinuation of Medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat; OLE = open label extension; PK = pharmacokinetic; PP = per protocol.
Note: Percentages are n/Number of subjects in the ITT Population within randomized treatment group and overall*100. The ITT population includes all randomized subjects. The Safety population includes all subjects who are randomized to treatment and receive at least 1 application of study drug in the Double-blind Period. The mITT population includes all subjects in the Safety population with at least 1 postbaseline assessment of efficacy in the Double-blind period. The PP population includes all 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. Completed continuing represents subjects who completed study visits and Double-blind treatment period (Day 90) and are continuing to OLE. Completed not continuing represents subjects who completed study visits and Double-blind treatment period (Day 90) but are not continuing to OLE. Early discontinuation of medication represent subjects who did not complete treatment but are not withdrawn from study (i.e., still in follow-up). Early termination from study represents subjects who did not complete study visits or complete the Double-blind treatment period.
SOURCE: Listing 16.2.1

Table 14.1.1.1 (cont.)
Summary of Subject Disposition
ITT Population

Category	Trifarotene cream HE1 100 ug/g (N=XXX)	Trifarotene cream HE1 200 ug/g (N=XXX)	Vehicle (N=XXX)	Overall (N=XXX)
Early Termination from Study	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for Early Termnation:				
Adverse Event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Intercurrent Illness	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lack of Efficacy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lost to Follow-up	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Non-compliance with Study Procedures	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Administrative Reasons	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Physician Decision	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Pregnancy	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Protocol Violation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subject Meets an Exclusion Criteria	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Withdrawal by Subject	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subject Withdrew Consent	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Study Terminated by Sponsor	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Blind Broken	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat; OLE = open label extension; PK = pharmacokinetic; PP = per protocol.
Note: Percentages are n/Number of subjects in the ITT Population within randomized treatment group and overall*100. The ITT population includes all randomized subjects. The Safety population includes all subjects who are randomized to treatment and receive at least 1 application of study drug in the Double-blind Period. The mITT population includes all subjects in the Safety population with at least 1 postbaseline assessment of efficacy in the Double-blind period. The PP population includes all 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. Completed continuing represents subjects who completed study visits and Double-blind treatment period (Day 90) and are continuing to OLE. Completed not continuing represents subjects who completed study visits and Double-blind treatment period (Day 90) but are not continuing to OLE. Early discontinuation of medication represent subjects who did not complete treatment but are not withdrawn from study (i.e., still in follow-up). Early termination from study represents subjects who did not complete study visits or complete the Double-blind treatment period.
SOURCE: Listing 16.2.1

Programming note: *Only include the Ongoing in Double-blind Study row when the overall n>0 for that row (i.e. dry runs).*

Table 14.1.1.2
Summary of Subject Disposition
OLE ITT Population

Category	Trifarotene cream HE1 200 ug/g (N=XXX)
OLE ITT Population	XX (XX.X%)
OLE Safety Population	XX (XX.X%)
OLE mITT Population	XX (XX.X%)
OLE PP Population	XX (XX.X%)
Completed	XX (XX.X%)
Ongoing in OLE Study	XX (XX.X%)
Early Discontinuation of Medication	XX (XX.X%)
Early Termination from Study	XX (XX.X%)
Reason for Early Termnation:	
Adverse Event	XX (XX.X%)
Intercurrent Illness	XX (XX.X%)
Death	XX (XX.X%)
Lack of Efficacy	XX (XX.X%)
Lost to Follow-up	XX (XX.X%)
Non-compliance with Study Procedures	XX (XX.X%)
Administrative Reasons	XX (XX.X%)
Physician Decision	XX (XX.X%)
Pregnancy	XX (XX.X%)
Protocol Violation	XX (XX.X%)
Subject Meets an Exclusion Criteria	XX (XX.X%)
Withdrawal by Subject	XX (XX.X%)
Subject Withdrew Consent	XX (XX.X%)
Study Terminated by Sponsor	XX (XX.X%)
Other	XX (XX.X%)

Abbreviations: EOT = end of treatment; ITT = intent-to-treat; mITT = modified intent-to-treat; OLE = open label extension; PP = per protocol.
Note: Percentages are n/Number of subjects in the OLE ITT Population within treatment group and overall*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE. The OLE ITT population includes all subjects who complete the 90-day Double-blind treatment Period and sign the OLE informed consent. The OLE Safety population includes all subjects who complete the 90-day Double-blind treatment Period and receive at least 1 application of study drug in the OLE. The OLE mITT population includes all subjects in the Safety population with at least 1 assessment of efficacy in after Visit 6 (Day 90). The OLE PP population includes 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. Completed continuing represents subjects who completed study visits and OLE treatment period. Early discontinuation of medication represent subjects who did not complete treatment but are not withdrawn from study (i.e., still in follow-up). Early termination from study represents subjects who did not complete study visits or complete the OLE treatment period.
SOURCE: Listing 16.2.1

Table 14.1.2.1
Summary of Demographics and Baseline Characteristics
ITT Population

Variable Statistic or Category	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Age (years)				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Sex				
Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Child-bearing Age? [1]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ethnicity [2]				
Hispanic or Latino	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Hispanic or Latino	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Applicable	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Race [2]				
American-Indian or Alaska Native	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Asian	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Black or African-American	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Native Hawaiian or Other Pacific Islander	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
White	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
More than One Race	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Race not Provided	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: IGA = Investigator's Global Assessment; SD = standard deviation.
Note: Percentages are n/Number of subjects in the ITT Population within randomized treatment group and overall*100.
[1] Only captured for female subjects; percentages are based on the number of female subjects in the Safety Population.
[2] Not captured in France.
SOURCE: Listings 16.2.4.1, 16.2.6.1

Table 14.1.2.1(cont.)
Summary of Demographics and Baseline Characteristics
ITT Population

Variable Statistic or Category	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Height (cm)				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Weight (kg)				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Body Mass Index (kg/m^2)				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
IGA Score				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Abbreviations: IGA = Investigator's Global Assessment; SD = standard deviation.
Note: Percentages are n/Number of subjects in the ITT Population within randomized treatment group and overall*100.
[1] Only captured for female subjects; percentages are based on the number of female subjects in the Safety Population.
[2] Not captured in France.
SOURCE: Listings 16.2.4.1, 16.2.6.1

Table 14.1.2.2
Summary of Demographics and Baseline Characteristics
OLE ITT Population

Same shell as Table 14.1.2.1
Programming note: *Only include one column for Trifarotene cream HE1 200 ug/g.*
*Update Note: to read "Percentages are n/Number of subjects in the OLE ITT Population within treatment group and overall*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."*
Add OLE = open label extension to Abbreviations.

Table 14.1.3
Summary of Medical Histories by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Subjects with at least 1 Recorded Medical History	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.
Note: Percentages are n/Number of subjects in the Safety population within actual treatment group and overall*100. Medical histories are coded using MedDRA version 21.1. Subjects were counted once for each system organ class (SOC) and once for each preferred term (PT). Medical history terms are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.4.3

Programming note: *SOC & PT text should be in title case in table, as shown in the shell.*

Table 14.1.4
Summary of Prior Medications by ATC Class Level 4 and Preferred Term
Safety Population

ATC Class Level 4 Preferred Term (ATC Class Level 5)	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Subjects with at least 1 Prior Medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC Class 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: ATC = Anatomic Therapeutic Chemical; PT = preferred term; WHO-DDE = World Health Organization-Drug Dictionary Enhanced.
Note: Percentages are n/Number of subjects in the Safety population within actual treatment group and overall*100. Medications were coded using WHO-DDE version March 2019. Prior medications are all medications that were started before the first dose of study drug. Medications are displayed by descending frequency of ATC Level 4 classification, by PT within ATC, and then alphabetically by PT, based on the overall column. Subjects were counted only once for each ATC and PT.
SOURCE: Listing 16.2.9.5

Programming note: *ATC & PT text should be in title case in table, as shown in the shell.*

Table 14.1.5.1
Summary of Drug Accountability (Drug Returned and Dispensed)
Safety Population

Visit Parameter Statistic	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Baseline [1]				
Total Weight of Tubes Dispensed (g)				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Day 14				
Total Weight of Tubes Dispensed (g)				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Total Number of Tubes Returned				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Abbreviation: OLE = open label extension. SD = standard deviation.
Note: Subjects are summarized by actual treatment group. Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the Double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the OLE.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listings 16.2.5.1, 16.2.5.2, 16.2.5.3

Table 14.1.5.1 (cont.)
Summary of Drug Accountability (Drug Returned and Dispensed)
Safety Population

Visit Parameter Statistic	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Day 14				
Total Number of Tubes Returned Unused				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Total Weight of Tubes Returned (g)				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX

Abbreviation: OLE = open label extension. SD = standard deviation.
Note: Subjects are summarized by actual treatment group. Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the Double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the OLE.
SOURCE: Listings 16.2.5.1, 16.2.5.2, 16.2.5.3

Programming note: *Continue for Day 30, Day 60, and Day 90.*

Table 14.1.5.2
Summary of Drug Accountability (Drug Returned and Dispensed)
OLE Safety Population

Same shell as Table 14.1.5.1

Programming note: *Only include one column for Trifarotene cream HE1 200 ug/g.*

Continue for Day 104, Day 120, Day 150 and Day 180.

Update Note: to read "Note: Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."

Table 14.1.5.3
Summary of Treatment Exposure and Compliance
Safety Population

Variable Statistic or Category	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Compliance by Tube Weight (%) [1]				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Compliant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Compliant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Compliance by Number of Doses (%) [2]				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Compliant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Compliant	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviation: SD = standard deviation.
Note: Percentages are n/Number of subjects in the Safety population within actual treatment group and overall*100. A subject is compliant with study product if he or she takes at least 80%-120% of the scheduled doses as assessed by diary entries, supplemented by tube weight.
[1] Compliance by tube weight = total weight used / total weight of tubes dispensed *100%, where total weight used = total weight of tubes dispensed (grams) – total weight of tubes returned (grams)
[2] Compliance by number of doses = number of doses taken / number of expected doses * 100%, where number of doses taken = total number of tubes dispensed – total number of tubes returned – total number of tubes returned unused, number of expected doses = 2 * number of weeks on study, and number of weeks on study = (last day on study – treatment start date + 1) / 7
SOURCE: Listings 16.2.5.1, 16.2.5.2, 16.2.5.3

Table 14.1.5.4
Summary of Treatment Exposure and Compliance
OLE Safety Population

Same shell as Table 14.1.5.3

Programming note: *Only include one column for Trifarotene cream HE1 200 ug/g.*

Update Note: to read "Note: Percentages are n/Number of subjects in the OLE Safety population within treatment group and overall*100. *All subjects received Trifarotene cream HE1 200 ug/g in the OLE."*

Add OLE = open label extension to Abbreviations.

Table 14.2.1.1.1
Primary Analysis: Logistic Regression Analysis of Successful Resolution of LI
ITT Population

Study Visit Statistic	Trifarotene cream HE1 100 ug/g (N = XX)	Trifarotene cream HE1 200 ug/g (N = XX)	Overall Trifarotene cream HE1 (N = XX)	Vehicle (N = XX)
Day 90				
n [1]	XX	XX	XX	XX
Successful Resolution [2]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Odds Ratio (Trifarotene cream HE1 vs Vehicle)	X.XX	X.XX	X.XX	
95% CI for Odds Ratio	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)	
P value [3]	X.XXX	X.XXX	X.XXX	
Difference in Proportion (Trifarotene cream HE1 vs Vehicle)	X.XX	X.XX	X.XX	
95% CI for Proportion Difference	(X.XX, X.XX)	(X.XX, X.XX)	(X.XX, X.XX)	
P value [3]	X.XXX	X.XXX	X.XXX	

Abbreviation: CI = confidence interval; EOT = end of treatment; IGA = Investigator's Global Assessment; ITT = intent to treat; LI = Lamellar Ichthyosis; OR = odds ratio.
Note: Percentages are n/Number of subjects in the ITT population within randomized treatment group*100. The 5-point (0 - 4) IGA is a measure of disease severity which considers both scaling and roughness. Higher IGA scores represent more severe disease.
[1] Number of subjects with an IGA assessment at each visit.
[2] Number of subjects with successful resolution of LI at a visit. Successful resolution is defined as clear/almost clear overall (IGA of 0 or 1, respectively) and at least a 2-grade change from Baseline on the
5-point (0 - 4) IGA scale. Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[3] Estimates for odds ratio, 95% CI for odds ratio, and P value are from a logistic regression model with treatment, baseline IGA score, and age group as factors. The odds ratio is the estimate of the odds of having successful resolution of LI for subjects treated with Trifarotene cream HE1 relative to that for subjects treated with vehicle. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years.
SOURCE: Listing 16.2.6.1

Programming note: *If Firth's penalized maximum likelihood is used, add 'Firth's penalized maximum likelihood estimation is used.' to end of 'Note:' footnote. If the treatment-by-age interaction is significant, include it in the logistic regression model and update footnote [3] to include this factor. After Day 90, repeat table for Days 14, 30, and 60.*

Table 14.2.1.1.2
Proportion of Subjects with Successful Resolution of LI in the OLE
OLE ITT Population

Study Visit Statistic	Trifarotene cream HE1 200 ug/g (N = XX)
Day 104	
n [1]	XX
Successful Resolution [2]	XX (XX.X%)
Day 120	
n [1]	XX
Successful Resolution [2]	XX (XX.X%)
Day 150	
n [1]	XX
Successful Resolution [2]	XX (XX.X%)
Day 180	
n [1]	XX
Successful Resolution [2]	XX (XX.X%)
Day 194	
n [1]	XX
Successful Resolution [2]	XX (XX.X%)

Abbreviation: CI = confidence interval; EOT = end of treatment; IGA = Investigator's Global Assessment; ITT = intent to treat; LI = Lamellar Ichthyosis; OLE = open label extension.
Note: Percentages are n/Number of subjects in the OLE ITT population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE. The 5-point (0 - 4) IGA is a measure of disease severity which considers both scaling and roughness. Higher IGA scores represent more severe disease.
[1] Number of subjects with an IGA assessment at each visit.
[2] Number of subjects with successful resolution of LI at a visit. Successful resolution is defined as clear/almost clear overall (IGA of 0 or 1, respectively) and at least a 2-grade change from Baseline on the 5-point (0 - 4) IGA scale. Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.6.1

Table 14.2.1.2.1
Primary Analysis, Sensitivity: Logistic Regression Analysis of Successful Resolution of LI
mITT Population

Same shell as Table 14.2.1.1.1
Programming note: *Update Abbreviations to remove ITT and include mITT = modified intent-to-treat.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the mITT population within randomized treatment group*100."*

Table 14.2.1.2.2
Proportion of Subjects with Successful Resolution of LI in the OLE
OLE mITT Population

Same shell as Table 14.2.1.1.2
Programming note: *Update Abbreviations to remove ITT and include mITT = modified intent-to-treat and OLE = open label extension.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the OLE mITT population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."*

Table 14.2.1.3.1
Primary Analysis, Sensitivity: Logistic Regression Analysis of Successful Resolution of LI
PP Population

Same shell as Table 14.2.1.1.1
Programming note: *Update Abbreviations to remove ITT and include PP = per protocol.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the PP population within actual treatment group*100."*

Table 14.2.1.3.2
Proportion of Subjects with Successful Resolution of LI in the OLE
OLE PP Population

Same shell as Table 14.2.1.1.2
Programming note: *Update Abbreviations to remove ITT and include OLE = open label extension and PP = per protocol.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the OLE PP population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."*

Table 14.2.1.4
Primary Analysis, Sensitivity: Logistic Regression Analysis of Successful Resolution of LI Using Multiple Imputation
ITT Population

Same shell as Table 14.2.1.1.1
Programming note: *Update footnote [3] to read "Estimates for odds ratio, 95% CI for odds ratio, and P value are from a logistic regression model with treatment, baseline IGA score, and age group as factors. The odds ratio is the estimate of the odds of having successful resolution of LI for subjects treated with Trifarotene cream HE1 relative to that for subjects treated with vehicle. Missing values were considered MNAR and imputed using MI with a placebo-based pattern mixture model and then categorized as treatment success. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years.*"

Table 14.2.1.5.1
Logistic Regression Analysis of 50% Reduction in IGA score from Baseline
ITT Population

Same shell as Table 14.2.1.1.1
Programming note: Update "Successful Resolution [2]" row text to read "50% Reduction from Baseline [2]".
Update footnote [2] to read "Number of subjects with a 50% reduction in IGA score from baseline at a visit. Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period. Higher IGA scores represent more severe disease."
Update [3] to read "Estimates for odds ratio, 95% CI for odds ratio, and P value are from a logistic regression model with treatment, baseline IGA score, and age group as factors. The odds ratio is the estimate of the odds of having a 50% reduction in IGA score from baseline for subjects treated with Trifarotene cream HE1 relative to that for subjects treated with vehicle. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."

Table 14.2.1.5.2
Proportion of Subjects with a 50% Reduction in IGA score from Baseline
OLE ITT Population

Same shell as Table 14.2.1.1.2
Programming note: Update "Successful Resolution [2]" row text to read "50% Reduction from Baseline [2]".
*Update Note: to read "Note: Percentages are n/Number of subjects in the OLE ITT population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."*
Update footnote [2] to read "Number of subjects with a 50% reduction in IGA score from baseline at a visit. Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period. Higher IGA scores represent more severe disease."

Table 14.2.1.6.1
MMRM Analysis of Change from Baseline in IGA Score
ITT Population

Study Visit	Trifarotene cream HE1 100 ug/g (N=XXX)		Trifarotene cream HE1 200 ug/g (N=XXX)	
Statistic [1]	Observed	CFB	Observed	CFB
Baseline [2]				
n	XXX		XXX	
Mean (SD)	XX.XX (XX.XXX)		XX.XX (XX.XXX)	
Median	XX.XX		XX.XX	
Min, Max	XX.X, XX.X		XX.X, XX.X	
Day 14				
n	XXX	XXX	XXX	XXX
Mean (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Median	XX.XX	XX.XX	XX.XX	XX.XX
Min, Max	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
LS Mean (SE) CFB		X.XX (X.XXX)		X.XX (X.XXX)
95% CI for LS Mean CFB		(X.XX, X.XX)		(X.XX, X.XX)
P value for CFB = 0		X.XXXX		X.XXXX
Comparison vs. Vehicle				
Difference in LS Mean (SE)		X.XX (X.XXX)		X.XX (X.XXX)
95% CI for Difference in LS Mean		(X.XX, X.XX)		(X.XX, X.XX)
P value for Difference		X.XXXX		X.XXXX

Abbreviations: CFB = change from baseline; CI = confidence interval; IGA = Investigator's Global Assessment; ITT = intent to treat; LS = least-squares; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error.
Note: Subjects are summarized by randomized treatment group. The 5-point (0 - 4) IGA is a measure of disease severity which considers both scaling and roughness. Higher IGA scores represent more severe disease.
[1] LS mean CFB, LS mean differences (Trifarotene cream HE1 - vehicle), 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in IGA score as the repeated dependent variable, fixed effect terms for baseline IGA score, treatment, study visit, treatment-by-study visit interaction, and age group as independent variables. An unstructured covariance matrix was used to model the within-subject correlation. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years.
[2] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.6.1

Programming note: *If the unstructured covariance structure does not converge, use other structures as outlined in the SAP section 8.1 and update the footnote accordingly. Include Days 30, 60, and 90 as well. Rows will be the same as what is displayed for Day 14. Repeat Table for Overall Trifarotene cream HE1 and Vehicle columns. Vehicle column will not have Comparison vs. Vehicle row cells populated.*

Table 14.2.1.6.2
MMRM Analysis of Change from Baseline in IGA Score
OLE ITT Population

Programming note: *Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."*
Only include one set of columns for Trifarotene cream HE1 200 ug/g.
Do not include Comparison vs. Vehicle rows.
Baseline [2], Days 104, 120, 150, 180, and 194 will be displayed.
Update footnote [1] to read "LS mean CFB, 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in IGA score as the repeated dependent variable, fixed effect terms for baseline IGA score, study visit, and age group as independent variables. An unstructured covariance matrix was used to model the within-subject correlation. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."

Table 14.2.7.1.1
Categorical IGA Scores
ITT Population

Study Visit Category	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XXX)
Baseline [1]				
0 = Clear	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
1 = Almost clear	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
2 = Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
3 = Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
4 = Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Day 14				
0 = Clear	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
1 = Almost clear	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
2 = Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
3 = Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
4 = Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
…				
Day 90				
0 = Clear	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
1 = Almost clear	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
2 = Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
3 = Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
4 = Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: IGA = Investigator's Global Assessment; ITT = intent to treat;
Note: Percentages are n/Number of subjects in the ITT population within randomized treatment group*100. The 5-point (0 - 4) IGA is a measure of disease severity which considers both scaling and roughness. Higher IGA scores represent more severe disease.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.6.1

Table 14.2.1.7.2
Categorical IGA Scores
OLE ITT Population

Programming note: *Update Note: to read "Percentages are n/Number of subjects in the OLE ITT population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."*
Only include one set of columns for Trifarotene cream HE1 200 ug/g.
Baseline [2], Days 104, 120, 150, 180, and 194 will be displayed.
Add OLE = open label extension to Abbreviations.

Table 14.2.2.1
Secondary Analysis: MMRM Analysis of Change from Baseline in VIIS Score
ITT Population

Same shell as Table 14.2.1.6.1

Programming note: *Update Note: to read "Note: Subjects are summarized by randomized treatment group. The VIIS is scored on a 5-point (0 - 4) scale by body area (chest/abdomen, back, legs, and arms). Higher VIIS scores represent worse scaling."*
Update [1] to read "LS mean CFB, LS mean differences (Trifarotene cream HE1 - vehicle), 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in VIIS score as the repeated dependent variable, fixed effect terms for baseline VIIS score, treatment, study visit, treatment-by-study visit interaction, and age group as independent variables. An unstructured covariance matrix was used to model the within-subject correlation. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."
Remove IGA and add VIIS= Visual Index for Ichthyosis Severity to Abbreviations.
Update SOURCE: to Listing 16.2.6.2

Table 14.2.2.2
MMRM Analysis of Change from Baseline in VIIS Score
OLE ITT Population

Same shell as Table 14.2.2.1
Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."
Only include one set of columns for Trifarotene cream HE1 200 ug/g.
Do not include Comparison vs. Vehicle rows.
Baseline [2], Days 104, 120, 150, 180, and 194 will be displayed.
Update footnote [1] to read "LS mean CFB, 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in IGA score as the repeated dependent variable, fixed effect terms for baseline IGA score, study visit, and age group as independent variables. An unstructured covariance matrix was used to model the within-subject correlation. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."
Update SOURCE: to Listing 16.2.6.2

Table 14.2.3.1
Secondary Analysis: MMRM Analysis of Change from Baseline in Individual Score for Roughness
ITT Population

Same shell as Table 14.2.1.6.1

Programming note: *Update Note: to read "Note: Subjects are summarized by randomized treatment group. The individual score for roughness measures the amount of roughness of the skin overall and is scored on a 5-point (0 - 4) scale. Higher scores indicate more severe roughness."*
Update footnote [1] to read "LS mean CFB, LS mean differences (Trifarotene cream HE1 - vehicle), 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in individual score for roughness as the repeated dependent variable, fixed effect terms for baseline individual score for roughness, treatment, study visit, treatment-by-study visit interaction, and age group as independent variables. An unstructured covariance matrix was used to model the within-subject correlation.
[2] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."
Update SOURCE: to Listing 16.2.6.3

Table 14.2.3.2
MMRM Analysis of Change from Baseline in Individual Score for Roughness
OLE ITT Population

Same shell as Table 14.2.1.6.1
Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE. The individual score for roughness measures the amount of roughness of the skin overall and is scored on a 5-point (0 - 4) scale. Higher scores indicate more severe roughness."
Only include one set of columns for Trifarotene cream HE1 200 ug/g.
Do not include Comparison vs. Vehicle rows.
Baseline [2], Days 104, 120, 150, 180, and 194 will be displayed.
Update footnote [1] to read "LS mean CFB, 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in individual score for roughness as the repeated dependent variable, fixed effect terms for baseline individual score for roughness, study visit, and age group as independent variables. An unstructured covariance matrix was used to model the within-subject correlation. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."
Update SOURCE: to Listing 16.2.6.3

Table 14.2.3.3
Logistic Regression Analysis of 2-grade Change in Individual Score for Roughness from Baseline
ITT Population

Same shell as Table 14.2.1.1.1
Programming note: *Update "Successful Resolution [2]" row text to read "2-grade Change from Baseline [2]".*
*Update Note: to read "Note: Percentages are n/Number of subjects in the ITT population within randomized treatment group*100. The individual score for roughness measures the amount of roughness of the skin overall and is scored on a 5-point (0 - 4) scale. Higher scores indicate more severe roughness."*
Update footnote [2] to read "Number of subjects with a 2-grade change in individual score for roughness from baseline at a visit. Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period. Higher scores indicate more severe roughness."
Update [3] to read "Estimates for odds ratio, 95% CI for odds ratio, and P value are from a logistic regression model with treatment, baseline individual score for roughness, and age group as factors. The odds ratio is the estimate of the odds of having a 2-grade change in individual score for roughness from baseline for subjects treated with Trifarotene cream HE1 relative to that for subjects treated with vehicle. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."
Update SOURCE: to Listing 16.2.6.3

Table 14.2.4.1
Secondary Analysis: MMRM Analysis of Change from Baseline in Palm/Sole Assessment
ITT Population

Same shell as Table 14.2.1.6.1

Programming note: *Update Note: to read "Note: Subjects are summarized by randomized treatment group. Thickening of the skin on the palms and soles will be measured on a 5-point (0 - 4) scale. Higher scores indicate more severe thickening."*
Update footnote [1] to read "LS mean CFB, LS mean differences (Trifarotene cream HE1 - vehicle), 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in palm/sole assessment score as the repeated dependent variable, fixed effect terms for baseline palm/sole assessment score, treatment, study visit, treatment-by-study visit interaction, and age group as independent variables. An unstructured covariance matrix was used to model the within-subject correlation.
[2] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."
Update SOURCE: to Listing 16.2.6.4

Table 14.2.4.2
MMRM Analysis of Change from Baseline in Palm/Sole Assessment
OLE ITT Population

Same shell as Table 14.2.1.6.1

Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE. Thickening of the skin on the palms and soles will be measured on a 5-point (0 - 4) scale. Higher scores indicate more severe thickening."
Only include one set of columns for Trifarotene cream HE1 200 ug/g.
Do not include Comparison vs. Vehicle rows.
Baseline [2], Days 104, 120, 150, 180, and 194 will be displayed.
Update footnote [1] to read "LS mean CFB, 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in palm/sole assessment score as the repeated dependent variable, fixed effect terms for baseline palm/sole assessment score, study visit, and age group as independent variables. An unstructured covariance matrix was used to model the within-subject correlation. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."
Update SOURCE: to Listing 16.2.6.4

Table 14.2.4.3
Logistic Regression Analysis of 2-grade Change in Palm/Sole Assessment from Baseline
ITT Population

Same shell as Table 14.2.1.1.1

Programming note: *Update "Successful Resolution [2]" row text to read "2-grade Change from Baseline [2]".*
*Update Note: to read "Note: Percentages are n/Number of subjects in the ITT population within randomized treatment group*100. Thickening of the skin on the palms and soles will be measured on a 5-point (0 - 4) scale. Higher scores indicate more severe thickening."*
Update footnote [2] to read "Number of subjects with a 2-grade change in palm/sole assessment score from baseline at a visit. Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period. Higher scores indicate more severe roughness."
Update [3] to read "Estimates for odds ratio, 95% CI for odds ratio, and P value are from a logistic regression model with treatment, baseline palm/sole assessment score, and age group as factors. The odds ratio is the estimate of the odds of having a 2-grade change in palm/sole assessment score from baseline for subjects treated with Trifarotene cream HE1 relative to that for subjects treated with vehicle. Age group is defined as adolescents (ages 12 to 17 years, inclusive) and adults ≥18 years."
Update SOURCE: to Listing 16.2.6.4

Table 14.2.5.1
Secondary Analysis: MMRM Analysis of Change from Baseline in Dermatology Life Quality Index
ITT Population

Same shell as Table 14.2.1.6.1

Programming note: *Update Note: to read "Note: Subjects are summarized by randomized treatment group. DLQI total score is derived as the sum of the 10 individual item scores, with a range of 0 to 30. Higher scores indicate poorer quality of life."*
Update footnote [1] to read "LS mean CFB, LS mean differences (Trifarotene cream HE1 - vehicle), 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in DLQI score as the repeated dependent variable, fixed effect terms for baseline DLQI score, treatment, study visit, and treatment-by-study visit interaction as independent variables. An unstructured covariance matrix was used to model the within-subject correlation.
[2] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period."
Update SOURCE: to Listing 16.2.6.5.1

Table 14.2.5.2
Secondary Analysis: MMRM Analysis of Change from Baseline in Children's Dermatology Life Quality Index
ITT Population

Same shell as Table 14.2.1.6.1

Programming note: *Update Note: to read "Note: Subjects are summarized by randomized treatment group. cDLQI total score is derived as the sum of the 10 individual item scores, with a range of 0 to 30. Higher scores indicate poorer quality of life."*
Update footnote [1] to read "LS mean CFB, LS mean differences (Trifarotene cream HE1 - vehicle), 95% CIs, and P values were obtained from a mixed model for repeated measures (MMRM) with change from baseline in cDLQI score as the repeated dependent variable, fixed effect terms for baseline cDLQI score, treatment, study visit, and treatment-by-study visit interaction as independent variables. An unstructured covariance matrix was used to model the within-subject correlation.
[2] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period."
Update SOURCE: to Listing 16.2.6.5.2

Table 14.2.6.1.1
Secondary Analysis: Presence of Fissures on Palms or Soles
ITT Population

Study Visit Category/Statistic [1]	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XXX)
Baseline [2]				
Fissures Present	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No Fissures Present	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Day 14				
Fissures Present	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No Fissures Present	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Comparison vs. Vehicle				
Difference in Percentage of Fissures Present	XX.X	XX.X	XX.X	
95% CI for Difference in Percentage of Fissures Present	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)	
P value for Difference	X.XXXX	X.XXXX	X.XXXX	
…				
Day 90				
Fissures Present	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No Fissures Present	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Comparison vs. Vehicle				
Difference in Percentage of Fissures Present	XX.X	XX.X	XX.X	
95% CI for Difference in Percentage of Fissures Present	(XX.X, XX.X)	(XX.X, XX.X)	(XX.X, XX.X)	
P value for Difference	X.XXXX	X.XXXX	X.XXXX	

Abbreviations: CI = confidence interval; ITT = intent-to-treat.
Note: Percentages are n/Number of subjects in the ITT population within randomized treatment group*100.
[1] P value from 2-sided Pearson's Chi-Square test. Difference is calculated Trifarotene cream HE1 - vehicle.
[2] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.6.6

Programming Note: *If cell counts are <5, use Fisher's Exact Test and update footnote [1] accordingly. Include all study visits (Days 14, 30, and 60).*

Table 14.2.6.1.2
Presence of Fissures on Palms or Soles
OLE ITT Population

Study Visit Category/Statistic	Trifarotene cream HE1 200 ug/g
Baseline [1]	
Fissures Present	XX (XX.X%)
No Fissures Present	XX (XX.X%)
Day 104	
Fissures Present	XX (XX.X%)
No Fissures Present	XX (XX.X%)
Day 120	
Fissures Present	XX (XX.X%)
No Fissures Present	XX (XX.X%)
Day 150	
Fissures Present	XX (XX.X%)
No Fissures Present	XX (XX.X%)
Day 180	
Fissures Present	XX (XX.X%)
No Fissures Present	XX (XX.X%)
Day 194	
Fissures Present	XX (XX.X%)
No Fissures Present	XX (XX.X%)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OLE = open label extension.
Note: Percentages are n/Number of subjects in the OLE ITT population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.6.6

Table 14.2.6.2.1
Secondary Analysis: Summary of Number of Fissures and Fissure Pain Level
ITT Population

Body Area: Palms

Study Visit Category/Statistic	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XXX)
Baseline [1]				
Number of Fissures				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Fissure Pain Level	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
None	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
…				
Day 90	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Number of Fissures				
n	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX
Fissure Pain Level	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
None	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: CI = confidence interval; ITT = intent-to-treat.
Note: Percentages are n/Number of subjects in the ITT population within randomized treatment group*100.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.6.6

Programming note: *Repeat for Body Area: Soles. Include all study visits (Days 14, 30, and 60).*

Table 14.2.6.2.2
Summary of Number of Fissures and Fissure Pain Level
OLE ITT Population

Same shell as Table 14.2.6.2.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the OLE ITT population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."*
Baseline [2], Days 104, 120, 150, 180, and 194 will be displayed.
Add OLE = open label extension to Abbreviations.

Table 14.2.7.1
Exploratory Analysis: Summary of Change from Baseline in Ectropion Score
ITT Population

Study Visit	Trifarotene cream HE1 100 ug/g (N=XXX)		Trifarotene cream HE1 200 ug/g (N=XXX)	
Statistic	Observed	CFB	Observed	CFB
Baseline [1]				
n	XXX		XXX	
Mean (SD)	XX.XX (XX.XXX)		XX.XX (XX.XXX)	
Median	XX.XX		XX.XX	
Min, Max	XX.X, XX.X		XX.X, XX.X	
Day 14				
n	XXX	XXX	XXX	XXX
Mean (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Median	XX.XX	XX.XX	XX.XX	XX.XX
Min, Max	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
…				
Day 90				
n	XXX	XXX	XXX	XXX
Mean (SD)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)	XX.XX (XX.XXX)
Median	XX.XX	XX.XX	XX.XX	XX.XX
Min, Max	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X

Abbreviations: CFB = change from baseline; ITT = intent to treat; SD = standard deviation.
Note: Subjects are summarized by randomized treatment group. Ectropion total score is derived as the sum of the 8 individual item scores (lateral apposition, medial apposition, scleral show, conjunctival show, excess tear film, redness of the eye, round canthus, punctum lacrimale), with a range of 0 to 8. Each individual item is scored 0 (nonaffected/no/invisible), 0.5 (≤ 1 mm/emerging), or 1 (affected/yes/visible). Higher scores indicates worse ectropion.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.6.7

Programming note: *Include Days 30, and 60 as well. Repeat Table for Overall Trifarotene cream HE1 and Vehicle columns.*

Table 14.2.7.2
Summary of from Baseline in Ectropion Score
OLE ITT Population

Same shell as 14.2.7.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the OLE ITT population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE."*
Baseline [2], Days 104, 120, 150, 180, and 194 will be displayed.
Add OLE = open label extension to Abbreviations.

Table 14.2.8.1
Exploratory Analysis: Change from Baseline in EQ-5D-5L
ITT Population

Same Shell as Table 14.2.7.1

Programming Note: *Headers will be as follows. Repeat for the following Parameters: Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression, and Your Health Today.*

Parameter: Mobility

	Trifarotene cream HE1 100 ug/g (N=XXX)		Trifarotene cream HE1 200 ug/g (N=XXX)	
Study Visit				
Statistic	Observed	CFB	Observed	CFB

Update Note: to read "Subjects are summarized by randomized treatment group. The EQ-5D is a measure of health related quality of life. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS). The EQ-5D-5L is intended for use in adult subjects. 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. Add VAS = visual analog scale to Abbreviations. Update SOURCE: to Listing 16.2.6.8

Table 14.2.8.2
Exploratory Analysis: Change from Baseline in EQ-5D-Y
ITT Population

Same Shell as Table 14.2.7.1

Programming Note: *Headers will be as follows. Repeat for the following Parameters: Taking Care of Myself, Doing Usual Activities, Having Pain or Discomfort, Feeling Worried, Sad or Unhappy, Number Subject Indicated on Scale.*

Parameter: Mobility

	Trifarotene cream HE1 100 ug/g (N=XXX)		Trifarotene cream HE1 200 ug/g (N=XXX)	
Study Visit				
Statistic	Observed	CFB	Observed	CFB

Update Note: to read "Subjects are summarized by randomized treatment group. The EQ-5D is a measure of health related quality of life. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS). The EQ-5D-Y is to be used for children and adolescents. 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. Add VAS = visual analog scale to Abbreviations. Update SOURCE: to Listing 16.2.6.8

Table 14.3.1.1.1
Overall Summary of Treatment Emergent Adverse Events during the Double-blind Period
Safety Population

Category	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Subjects with at least 1 TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with an SAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Maximum Severity of TEAE [1]					
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Relationship of TEAE [2]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with a TEAE Leading to Discontinuation of Study Drug	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with an AE leading to Death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: AE = adverse event; CRF = case report form; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment emergent adverse event.
Note: Percentages are n/Number of subjects in the Safety Population within actual treatment group and overall*100. AEs were coded using MedDRA version 21.1. A TEAE is any AE with an onset at the time of or following the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. This will include any AE starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first.
[1] Subjects are counted only once at the worst severity. If a severity designation is missing, it will be considered as severe.
[2] Subjects are counted only once at the strongest possible relationship. If a relationship designation is missing, the AE will be considered as related. This relationship is categorized for summarization as follows: Related = Related and Possibly Related; Not Related = Not Related and Unlikely Related.
SOURCE: Listing 16.2.7.1

Table 14.3.1.1.2
Overall Summary of Treatment Emergent Adverse Events during the OLE
OLE Safety Population

Same shell as Table 14.3.1.1.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the OLE Safety population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Add OLE = open label extension to Abbreviations.*

Table 14.3.1.2.1
Incidence of Treatment Emergent Adverse Events during the Double-blind Period by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Subjects with at least 1 TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event.
Note: Percentages are n/Number of subjects in the Safety Population within actual treatment group and overall*100. AEs were coded using MedDRA version 21.1. A TEAE is any AE with an onset at the time of or following the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. This will include any AE starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. Subjects are counted once for each system organ class (SOC) and once for each preferred term (PT). AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.7.1

Table 14.3.1.2.2
Incidence of Treatment Emergent Adverse Events during the OLE by System Organ Class and Preferred Term
OLE Safety Population

Same shell as 14.3.1.2.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the OLE Safety population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Add OLE = open label extension to Abbreviations.*

Table 14.3.1.3.1
Incidence of Treatment Emergent Adverse Events during the Double-blind Period by System Organ Class, Preferred Term, and Maximum Severity
Safety Population

System Organ Class Preferred Term Severity	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Subjects with at least 1 TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event.
Note: Percentages are n/Number of subjects in the Safety Population within actual treatment group and overall*100. AEs were coded using MedDRA version 21.1. A TEAE is any AE with an onset at the time of or following the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. This will include any AE starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. Subjects are counted once for each system organ class (SOC) and once for each preferred term (PT) at the maximum severity. The severity shown is the greatest severity reported for a particular subject (Severe > Moderate > Mild). AEs with a missing severity were counted as Severe. AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.7.1

Table 14.3.1.3.2
Incidence of Treatment Emergent Adverse Events during the OLE by System Organ Class, Preferred Term, and Maximum Severity
OLE Safety Population

Same shell as 14.3.1.3.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the OLE Safety population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Add OLE = open label extension to Abbreviations.*

Table 14.3.1.4.1
Incidence of Treatment Emergent Adverse Events during the Double-blind Period by System Organ Class, Preferred Term, and Relationship to Study Drug
Safety Population

System Organ Class Preferred Term Relationship [1]	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Subjects with at least 1 TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment emergent adverse event.
Note: Percentages are n/Number of subjects in the Safety Population within actual treatment group and overall*100. AEs were coded using MedDRA version 21.1. A TEAE is any AE with an onset at the time of or following the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. This will include any AE starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. Subjects are counted once for each system organ class (SOC) and once for each preferred term (PT) at the greatest relationship category. The relationship shown is the greatest relationship reported for a particular subject (Related > Not Related). AEs with a missing relationship were counted as Related. AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
[1] Related = Related and Possibly Related; Not Related = Not Related and Unlikely Related.
SOURCE: Listing 16.2.7.1

Table 14.3.1.4.2
Incidence of Treatment Emergent Adverse Events during the OLE by System Organ Class, Preferred Term, and Relationship to Study Drug
OLE Safety Population

Same shell as 14.3.1.4.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g.*
*Update Note: to read "Note: Percentages are n/Number of subjects in the OLE Safety population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Add OLE = open label extension to Abbreviations.*

Table 14.3.2.1.1
Incidence of Adverse Events Leading to Withdrawal during the Double-blind Period by SOC, PT, and Treatment
Safety Population

Same shell as Table 14.3.1.2.1

Programming note: *Update first row text to* "Subjects with at least 1 TEAE Leading to Withdrawal."

Table 14.3.2.1.2
Incidence of Adverse Events Leading to Withdrawal during the OLE by SOC, PT, and Treatment
OLE Safety Population

Same shell as Table 14.3.1.2.2

Programming note: *Update first row text to* "Subjects with at least 1 TEAE Leading to Withdrawal."

Table 14.3.2.2.1
Incidence of Serious Adverse Events during the Double-blind Period by SOC, PT, and Treatment
Safety Population

Same shell as Table 14.3.1.2.1

Programming note: *Update first row text to* "Subjects with at least 1 SAE." *Add SAE = serious adverse event to abbreviations.*

Table 14.3.2.2.2
Incidence of Serious Adverse Events during the OLE by SOC, PT, and Treatment
OLE Safety Population

Same shell as Table 14.3.1.2.2

Programming note: *Update first row text to* "Subjects with at least 1 SAE." *Add SAE = serious adverse event to abbreviations.*

Table 14.3.3.1.1
Listing of Adverse Events Leading to Withdrawal during the Double-blind Period
Safety Population

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	TEAE? [1]	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/Time (Study Day)/ End Date/Time (Study Day)	Severity/ Relationship to Study Drug	Outcome	Serious?/ Criteria Met	Action Taken/ Other Action Taken?
XXXXX	XXX	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX XXXXXXXXXXXXX	DDMMMYYYY/HH:MM (X)/ DDMMMYYYY/HH:MM (X)	XXXXXXXXX/ XXXXXXXXXX	XXXXXXXXX	XX	XXXXXXXXX/ XXXXXXXXX
XXXXX	XX	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX XXXXXXXXXXXXX	DDMMMYYYY/HH:MM (X)/ DDMONYYYY/HH:MM (X)	XXXXXXXXX/ XXXXXXXXXX	XXXXXXXXX	XX	XXXXXXXXX/ XXXXXXXXX
	XXX	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX XXXXXXXXXXXXX	DDMMMYYYY/HH:MM (X)/ Ongoing	XXXXXXXXX/ XXXXXXXXXX	XXXXXXXXX/	XXX/ XXXXXXXXX	XXXXXXXXX/ XXXXXXXXX

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.
Note: Study day is calculated relative to the date of first dose of study drug. AEs were coded using MedDRA version 21.1.
[1] A TEAE is any AE with an onset at the time of or following the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. This will include any AE starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first.

Programming note: *If time missing, display "- -:- -". If Serious? is Yes, concatenate all serious criteria marked as Yes with a semicolon. If Other Action Taken? Is Yes, concatenate Medication Required, Relevant Procedure, Procedure Specify, Other, or Other Specify with a colon as applicable. If no events meet the criteria for display, present "No events are reported." SOC & PT text should be in proper case in table.*

Table 14.3.3.1.2
Listing of Adverse Events Leading to Withdrawal during the OLE
OLE Safety Population

Same shell as Table 14.3.3.1.1

Programming note: *Add OLE = open label extension to Abbreviations.*

Table 14.3.3.2.1
Listing of Serious Adverse Events during the Double-blind Period
Safety Population

Same shell as Table 14.3.3.1.1

Table 14.3.3.2.2
Listing of Serious Adverse Events during the OLE
OLE Safety Population

Same shell as Table 14.3.3.1.1

Programming note: *Add OLE = open label extension to Abbreviations.*

Table 14.3.3.3.1
Listing of Deaths during the Double-blind Period
Safety Population

Same shell as Table 14.3.3.1.1

Table 14.3.3.3.1
Listing of Deaths during the OLE
OLE Safety Population

Same shell as Table 14.3.3.1.1

Programming note: *Add OLE = open label extension to Abbreviations.*

Table 14.3.4.1
Listing of Abnormal Laboratory Data
Safety Population and OLE Safety Population

Randomized Treatment: XXXXXXXXXXX

Subject ID	Parameter Category	Parameter (unit)	Study Visit	Date/Time of Assessment (Study Day)	Standard Results	Standard Reference Range [1]	Standard Reference Range Flag
XXXXX	Chemistry	Albumin (unit)	XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XX – YY	
			XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XX – YY	XXX
			XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XX – YY	
			XXXXXX		ND		
			XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XX – YY	

Abbreviations: AL = abnormal-low; AH = abnormal-high; ND = not done.
Note: Study day is calculated relative to the date of first dose of study drug. Assessments marked as Not Done are not presented.
[1] Reference range is used to identify potentially clinically significant laboratory values.

Programming note: *include all parameter categories and parameters.*

Table 14.3.5.1.1.1
Laboratory Data: Change from Baseline in Clinical Chemistry Parameters by Study Visit
Safety Population

Parameter: XXXXXXX (unit)

Study Visit / Statistic	Trifarotene cream HE1 100 ug/g (N=XX)		Trifarotene cream HE1 200 ug/g (N=XX)		Overall Trifarotene cream HE1 (N=XX)	
	Observed	CFB	Observed	CFB	Observed	CFB
Baseline [1]						
n	XX		XX		XX	
Mean (SD)	XX.X (XX.XX)		XX.X (XX.XX)		XX.X (XX.XX)	
Median	XX.X		XX.X		XX.X	
Min, Max	XX, XX		XX, XX		XX, XX	
Day 30						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Day 90						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

Repeat for all clinical chemistry parameters.

Abbreviation: CFB = change from baseline; SD = standard deviation.
Note: Subjects are summarized by actual treatment group and overall.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.8.1

Programming note: *Repeat table for Vehicle and Overall columns.*

Table 14.3.5.1.1.2
Laboratory Data: Change from Baseline in Clinical Chemistry Parameters by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits will be Baseline, Day 120, and Day 180. Add OLE = open label extension to Abbreviations.*

Table 14.3.5.1.2.1
Laboratory Data: Shift from Baseline in Clinical Chemistry Parameters by Study Visit
Safety Population

Parameter: XXXXXXX

	Baseline [1]			
	Trifarotene cream HE1 100 ug/g (N=XX)			
Study Visit Category	Low n (%)	Normal n (%)	High n (%)	Missing n (%)
Day 30				
Low	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
High	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Missing	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Day 90				
Low	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
High	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Missing	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Continue for other parameters. Sort alphabetically by parameter.

Note: Note: Percentages are n/Number of subjects in the Safety Population within actual treatment group and overall*100.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.8.1

Programming note: *Repeat table for Trifarotene cream HE1 200 ug/g, Overall Trifarotene cream HE1, Vehicle, and Overall treatment groups.*

Table 14.3.5.1.2.2
Laboratory Data: Shift from Baseline in Clinical Chemistry Parameters by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.2.1

Programming note: *Only include Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits will be Baseline, Day 120, and Day 180. Add OLE = open label extension to Abbreviations.*

Table 14.3.5.2.1.1
Laboratory Data: Change from Baseline in Hematology Parameters by Study Visit
Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Update SOURCE: to Listing 16.2.8.2*

Table 14.3.5.2.1.2
Laboratory Data: Change from Baseline in Hematology Parameters by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits will be Baseline, Day 120, and Day 180. Add OLE = open label extension to Abbreviations. Update SOURCE: to Listing 16.2.8.2*

Table 14.3.5.2.2.1
Laboratory Data: Shift from Baseline in Hematology Parameters by Study Visit
Safety Population

Same shell as Table 14.3.5.1.2.1

Programming note: *Update SOURCE: to Listing 16.2.8.2*

Table 14.3.5.2.2.2
Laboratory Data: Shift from Baseline in Hematology Parameters by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.2.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits will be Baseline, Day 120, and Day 180. Add OLE = open label extension to Abbreviations. Update SOURCE: to Listing 16.2.8.2*

Table 14.3.5.3.1.1
Laboratory Data: Change from Baseline in Coagulation Parameters by Study Visit
Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Update SOURCE: to Listing 16.2.8.3*

Table 14.3.5.3.1.2
Laboratory Data: Change from Baseline in Coagulation Parameters by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits will be Baseline, Day 120, and Day 180. Add OLE = open label extension to Abbreviations. Update SOURCE: to Listing 16.2.8.3*

Table 14.3.5.3.2.1
Laboratory Data: Shift from Baseline in Coagulation Parameters by Study Visit
Safety Population

Same shell as Table 14.3.5.1.2.1

Programming note: *Update SOURCE: to Listing 16.2.8.3*

Table 14.3.5.3.2.2
Laboratory Data: Shift from Baseline in Coagulation Parameters by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.2.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits will be Baseline, Day 120, and Day 180. Add OLE = open label extension to Abbreviations. Update SOURCE: to Listing 16.2.8.3*

Table 14.3.5.4.1.1
Laboratory Data: Change from Baseline in Quantitative Urinalysis Parameters by Study Visit
Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Update SOURCE: to Listing 16.2.8.4*

Table 14.3.5.4.1.2
Laboratory Data: Change from Baseline in Quantitative Urinalysis Parameters by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits will be Baseline, Day 120, and Day 180. Add OLE = open label extension to Abbreviations. Update SOURCE: to Listing 16.2.8.4*

Table 14.3.5.4.2.1
Laboratory Data: Shift from Baseline in Quantitative Urinalysis Parameters by Study Visit
Safety Population

Same shell as Table 14.3.5.1.2.1

Programming note: *Update SOURCE: to Listing 16.2.8.4*

Table 14.3.5.4.2.2
Laboratory Data: Shift from Baseline in Quantitative Urinalysis Parameters by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.2.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits will be Baseline, Day 120, and Day 180. Add OLE = open label extension to Abbreviations. Update SOURCE: to Listing 16.2.8.4*

Table 14.3.5.4.3.1
Laboratory Data: Summary of Qualitative Urinalysis Parameters by Study Visit
Safety Population

Parameter: XXXXXXX (unit)

Study Visit Category	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Baseline [1]					
Category 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Day 30					
Category 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Day 90					
Category 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Category 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: Percentages are n/Number of subjects in the ITT population within randomized treatment group and overall*100.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.8.4

Table 14.3.5.4.3.2
Laboratory Data: Summary of Qualitative Urinalysis Parameters by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.4.3.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits will be Baseline, Day 120, and Day 180. Add OLE = open label extension to Abbreviations.*

Table 14.3.6.1.1
Summary of Vital Signs by Study Visit
Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Visits include Baseline [1], Days 14, 30, 60, and 90. Parameters include weight (kg), BMI (kg/m^2), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg). Include derivation of BMI in Note: Body Mass Index (BMI) = weight (kg) / [height (m)]^2. Update SOURCE: to Listings 16.2.9.1*

Table 14.3.6.1.2
Summary of Vital Signs by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits include Baseline [1], Days 120, 180, and 194. Parameters include weight (kg), BMI (kg/m^2), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg). Include derivation of BMI in Note: Body Mass Index (BMI) = weight (kg) / [height (m)]^2. Add OLE = open label extension to Abbreviations. Update SOURCE: to Listings 16.2.9.1*

Table 14.3.6.2.1
Summary of 12-Lead Electrocardiogram by Study Visit
Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Visits include Baseline [1], Days 30 and 90. Parameters include heart rate (bpm), PR interval (ms), QRS interval (ms), uncorrected QT interval (ms), and QTcF (ms). Update SOURCE: to Listings 16.2.9.2*

Table 14.3.6.2.2
Summary of 12-Lead Electrocardiogram by Study Visit
OLE Safety Population

Same shell as Table 14.3.5.1.1.1

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits include Baseline [1], Days 120 and 180. Parameters include heart rate (bpm), PR interval (ms), QRS interval (ms), uncorrected QT interval (ms), and QTcF (ms). Add OLE = open label extension to Abbreviations. Update SOURCE: to Listings 16.2.9.2*

Table 14.3.6.2.3
Summary of 12-Lead Electrocardiogram Interpretation by Study Visit
Safety Population

Study Visit Category	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Baseline [1]					
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Day 30					
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Day 90					
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: Percentages are n/Number of subjects in the Safety population within actual treatment group and overall*100.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.9.2

Table 14.3.6.2.4
Summary of 12-Lead Electrocardiogram Interpretation by Study Visit
OLE Safety Population

Same shell as Table 14.3.6.2.3

Programming note: *Only include one set of columns for Trifarotene cream HE1 200 ug/g. Update Note: to read "Subjects are summarized by treatment group. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Visits include Baseline [1], Days 120 and 180.*

Table 14.3.6.3.1
Summary of Local Tolerability Assessments by Study Visit
Safety Population

Study Visit: XXXXX

Body Area Assessment Score	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Chest/Abdomen					
Erythema					
None	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Stinging/Burning					
None	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Pruritus					
None	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: Percentages are n/Number of subjects in the Safety population within actual treatment group and overall*100.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.2.9.3

Programming note: *Continue for Back, Arms, and Legs. Visits will be Baseline [1], Day 14, Day 30, Day 60, and Day 90.*

Table 14.3.6.3.2
Summary of Local Tolerability Assessments by Study Visit
OLE Safety Population

Same shell as Table 14.3.6.3.1

Programming note: *Continue for Back, Arms, and Legs. Visits will be Baseline [1], Day 104, Day 120, and Day 150. Update Note: to read "Note: Percentages are n/Number of subjects in the OLE Safety population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Add OLE = open label extension to Abbreviations.*

Table 14.3.6.4.1
Summary of Physical Examination Results by Study Visit
Safety Population

Study Visit: XXXXX

Body System Result Clinically Significant?	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)	Overall Trifarotene cream HE1 (N=XX)	Vehicle (N=XX)	Overall (N=XX)
Body System 1					
Not Done	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Body System 2					
Not Done	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Normal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Abnormal	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

…

Note: Percentages are n/Number of subjects in the Safety population within actual treatment group and overall*100.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
SOURCE: Listing 16.3.9.4

Programming note: *Continue for all body systems. Visits will be Baseline [1] and Day 90.*

Table 14.3.6.4.2
Summary of Physical Examination Results by Study Visit
OLE Safety Population

Same shell as Table 14.3.6.4.1

Programming note: *Visits will be Day 180 and Day 194. Update Note: to read "Note: Percentages are n/Number of subjects in the OLE Safety population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE." Add OLE = open label extension to Abbreviations.*

Table 14.3.6.5.1
Summary of Concomitant Medications during the Double-blind Period by ATC Class Level 4 and Preferred Term
Safety Population

Same shell as Table 14.1.4

Programming note: *Update Note: to read "Note: Percentages are n/Number of subjects in the Safety population within actual treatment group and overall*100. Medications were coded using WHO-DDE version March 2019. Concomitant medications are any medications continuing or starting after the first dose of study drug through the end of study. Medications are displayed by descending frequency of ATC Level 4 classification, by PT within ATC, and then alphabetically by PT, based on the overall column. Subjects were counted only once for each ATC and PT. Include an additional column for Overall Trifarotene cream HE1.*

Table 14.3.6.5.2
Summary of Concomitant Medications during the OLE by ATC Class Level 4 and Preferred Term
Safety Population

Same shell as Table 14.1.4

Programming note: *Update Note: to read "Note: Percentages are n/Number of subjects in the OLE Safety population within treatment group*100. All subjects received Trifarotene cream HE1 200 ug/g in the OLE. Medications were coded using WHO-DDE version March 2019. Concomitant medications are any medications continuing or starting after the first dose of study drug through the end of study. Medications are displayed by descending frequency of ATC Level 4 classification, by PT within ATC, and then alphabetically by PT, based on the overall column. Subjects were counted only once for each ATC and PT. Include an additional column for Overall Trifarotene cream HE1.*

Table 14.4.1.1
Summary of Pharmacokinetic Concentrations by Study Visit
PK Population

Study Visit Statistic	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)
Day 1, Pre-Dose		
n	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Geometric Mean	XX.X	XX.X
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
%CV	XX.X	XX.X
Day 1, 1 hour Post-Dose		
n	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Geometric Mean	XX.X	XX.X
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
%CV	XX.X	XX.X
Day 1, 2 Hours Post-Dose		
n	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Geometric Mean	XX.X	XX.X
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
%CV	XX.X	XX.X
…		

Abbreviation: BLQ = below limit of quantification; PK = pharmacokinetic; SD = standard deviation.
Note: Values below the lower limit of quantification (<BLQ) have been set to zero in the calculation of the summary statistics.
SOURCE: Listing 16.2.5.4.1, 16.2.5.4.2, 16.2.4.3

Programming note: *Time points will be pre-dose, 1, 2, 4, 8, 12, and 24 hours post dose on Day 1 and Day 30.*

Table 14.4.1.2
Summary of Pharmacokinetic Parameters
PK Population

Study Visit Statistic	Trifarotene cream HE1 100 ug/g (N=XX)	Trifarotene cream HE1 200 ug/g (N=XX)
$AUC_{(0-t)}$ (ng/mL*hr)		
n	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Geometric Mean	XX.X	XX.X
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
%CV	XX.X	XX.X
C_{max} (ng/mL)		
n	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Geometric Mean	XX.X	XX.X
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX
%CV	XX.X	XX.X
T_{max}		
Median	XX.X	XX.X
Min, Max	XX, XX	XX, XX

Abbreviation: AUC = area under the plasma concentration-time curve; BLQ = below limit of quantification; Cmax = peak plasma concentration; CV = coefficient of variation; λ_z = apparent terminal phase rate constant; PK = pharmacokinetic; SD = standard deviation; t1/2= first order termination half-life; Tmax = time of Cmax.
SOURCE: Listing 16.2.5.4.4

Programming note: *Continue for* AUC_{0-inf}, $t_{1/2}$, λ_z, if data permit. If not, do not include in abbreviations.

14.3. Planned Listing Shells

Listing 16.2.1
Subject Disposition
All Subjects

Randomized Treatment: XXXXXXXXX

		Double-blind Period				OLE		
Subject ID	Date Informed Consent Signed	Subject Status	Date of Completion/ Discontinuation (Study Day)	Reason for Early Termination	Was the Blind Broken For This Subject?	Subject Status	Date of Completion/ Discontinuation (Study Day)	Reason for Early Termination
XXXXXX	DDMMMYYYY	XXXXXX	DDMMMYYYY (XX)			XXXXXX	DDMMMYYYY (XX)	
XXXXXX	DDMMMYYYY	XXXXXX	DDMMMYYYY (XX)			XXXXXX	DDMMMYYYY (XX)	
XXXXXX	DDMMMYYYY	XXXXXX	DDMMMYYYY (XX)	XXXXXXXX: XXXXXX		XXXXXX	DDMMMYYYY (XX)	XXXXXXXX: XXXXXX
XXXXXX	DDMMMYYYY	XXXXXX	DDMMMYYYY (X)	XXXXXX		XXXXXX	DDMMMYYYY (X)	XXXXXX
XXXXXX	DDMMMYYYY	XXXXXX	DDMMMYYYY (XX)	XXXXXXXXXXXXXX	XXX; XXXXXX; XXXXX	XXXXXX	DDMMMYYYY (XX)	XXXXXXXXXXXXXX

Abbreviation: OLE = open label extension.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming Note: *Subject status will be completed continuing, completed not continuing, or early termination. If reason for early termination is AE, Physician Decision, Protocol Violation, or Other, concatenate the specify text as follows: "Other: XXXXXXXXX". If reason for early termination is lost to follow-up, concatenate with date of last contact and comments as follows: "Lost to follow-up; date of last contact: DDMMMYYYY; XXXXX". If reason for early termination is death, concatenate with comment, cause of death and date of death as follows: "Lost to follow-up; XXXXX; date of death: DDMMMYYYY; comment: XXXX".*

Listing 16.2.2.1
Inclusion and Exclusion Criteria
All Subjects

Randomized Treatment: XXXXXXX

Subject ID	Assessment Date (Study Day)	Met All Inclusion Criteria?	Inclusion Criteria Number(s) Not Met [1]	Met Any Exclusion Criteria?	Exclusion Criteria Number(s) Met [2]
XXXXXX	DDMMMYYYY (XX)	Yes		No	
XXXXXX	DDMMMYYYY (XX)	Yes		No	
XXXXXX	DDMMMYYYY (XX)	Yes		No	
XXXXXX	DDMMMYYYY (XX)	No	XX	No	
XXXXXX	DDMMMYYYY (XX)	Yes		No	
XXXXXX	DDMMMYYYY (XX)	Yes		Yes	XX; XX

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.
[1] XX = XXXXXXXXXXXXXXXXXXXXXXXX.
[2] XX = XXXXXXXXXXXXXXXXX; XX = XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.

Programming note: *If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma as shown above. Decode any relevant criteria in the footnotes as shown in the example. If no criteria are present for a column, remove the [1] and/or [2] from the column header.*

Listing 16.2.2.2
Screen Failures
All Subjects

Subject ID	Date of Screen Failure (Study Day)	Reason for Screen Failure	Other Reason for Screen Failure
XXXXXX	DDMMMYYYY (XX)	XXXXXX	XXXXXXXXXXXXXXX
XXXXXX	DDMMMYYYY (XX)	XXXXXX	
XXXXXX	DDMMMYYYY (XX)	XXXXXX	
XXXXXX	DDMMMYYYY (XX)	XXXXXX	XXXXXXXXXXXXX
XXXXXX	DDMMMYYYY (XX)	XXXXXX	
XXXXXX	DDMMMYYYY (XX)	XXXXXX	

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.2.3
Protocol Deviations
All Subjects

Randomized Treatment: XXXXXXXXXXX

Subject ID	Date Identified (Study Day)	Event Date (Study Day)	Study Visit	Event Type	Violation Level	Description	Action/Resolution	Reportable to IRB?	Excluded from PP Population?
XXXXXX	DDMMMYYYY (XX)	DDMMMYYYY (XX)	XXXXXX	XXXXXXXXXXX	MAJOR	XXXXXXX	XXXXXXX	XXX; DDMMMYYYY; XXXXX	XXX
	DDMMMYYYY (XX)	DDMMMYYYY (XX)	XXXXXX	XXXXXXXXXXXXX	MINOR	XXXXXXXXXXXXXXX	XXXXXXXXXXXXXXX		XXX
XXXXXX	DDMMMYYYY (XX)	DDMMMYYYY (XX)	XXXXXX	XXXXXXXXXXX	MINOR	XXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXX		XX
XXXXXX	DDMMMYYYY (X)	DDMMMYYYY (X)	XXXXXX	XXXXXXXXXXX	MAJOR	XXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXX		XX

Abbreviation: IRB = institutional review board; PP = per protocol.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming note: *the structure of this listing may change depending on the information in the protocol deviations file. If Reportable to IRB is yes, concatenate IRB Submission Date and IRB Submission Comments fields with a semicolon.*

Listing 16.2.3
Analysis Populations
All Subjects

Subject	Randomization			Actual	Analysis Populations					
ID	Date	Number	Treatment	Treatment	ITT/ OLE ITT [1]	mITT/ OLE mITT [2]	PP/ OLE PP [3]	Safety/ OLE Safety [4]	PK [5]	Primary Reason(s) for Exclusion
XXXXXX	DDMMMYYYY	XXXX	XXXXXXXXXXXX	XXXXXXXXXXXX	Yes	Yes	No	Yes	No	PP: Subject had a significant protocol violation.
XXXXXX	DDMMMYYYY	XXXX	XXXXXXXXXX	XXXXXXXXXX	Yes	Yes	Yes	Yes	Yes	
XXXXXX	DDMMMYYYY	XXXX	XXXXXXXXXX	XXXXXXXXXX	No	Yes	No	Yes	No	Safety: Subject did not receive at least one application of study drug.

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat; OLE = open label extension; PK= pharmacokinetic; PP = per protocol.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period.
[1] The ITT population includes all randomized subjects. The OLE ITT population includes all subjects who complete the 90-day Double-blind Treatment Period and sign the OLE informed consent.
[2] The mITT includes all subjects in the Safety population with at least 1 post baseline assessment of efficacy in the Double-blind Period. The OLE mITT population includes all subjects in the OLE Safety population with at least 1 assessment of efficacy after Visit 6.
[3] The PP Population includes 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 OLE PP population includes 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.
[4] The Safety Population includes all subjects who are randomized to treatment and receive at least 1 application of study drug in the Double-blind Period. The OLE Safety population includes all subjects who complete the 90-day Double-blind Treatment Period and receive at least 1 application of study drug in the OLE.
[5] The PK Population includes all subjects in the Safety population who have at least 1 plasma sample with quantifiable concentration.

Programming note: *Concatenate all reasons for exclusion with a colon.*

Listing 16.2.4.1
Subject Demographics
All Subjects

Randomized Treatment: XXXXXXX

Subject ID	Date of Birth	Age (years)	QOL Questionnaires Used	Sex	Child-Bearing Potential?	Ethnicity	Race	Weight (kg)	Height (cm)	BMI (mg/m^2) [1]
XXXXXX	DDMMMYYY	XX	XXXX	XXXX	No	XXXXXXX	XXXXXXX	XX.X	XX.X	XX.X
XXXXXX	DDMMMYYY	XX	XXXXXX	XXXXXX	No	XXXXXXX	XXXXXX	XX.X	XX.X	XX.X
XXXXXX	DDMMMYYY	XX	XXXXXX	XXXXXX	Yes	XXXXXXX	XXXXXX	XX.X	XX.X	XX.X
XXXXXX	DDMMMYYY	XX	XXXX	XXXX	No	XXXXXXX	XXXXX	XX.X	XX.X	XX.X
XXXXXX	DDMMMYYY	XX	XXXXXX	XXXXXX	No	XXXXXXX	XXXXXX	XX.X	XX.X	XX.X
XXXXXX	DDMMMYYY	XX	XXXX	XXXX	Yes	XXXXXX	XXXXXX	XX.X	XX.X	XX.X

Abbreviations: BMI = body mass index; QOL =quality of life.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Height and weight are values obtained at screening.
[1] BMI = weight (kg) / [height (m)]^2.

Listing 16.2.4.2
Informed Consent and Reconsent
All Subjects

Randomized Treatment: XXXXXXXXXXX

Subject ID	Screened Previously?	Previous Subject Number	Protocol Version of Initial Consent/Assent	Date Informed Consent/Assent Signed	Consent to PK Sub-study?	Signed Photographic ICF?	Re-consent to Later Protocol Version 2.0?	Date Reconsent	Date of Assent	Date OLE Informed Consent/Assent Signed
XXXXXX	No		X.X	DDMMMYYY	No	No	Yes	DDMMMYYY	DDMMMYYY	DDMMMYYY
XXXXXX	No		X.X	DDMMMYYY	No	No	Yes	DDMMMYYY	DDMMMYYY	DDMMMYYY
XXXXXX	Yes	XXXXXXX	X.X	DDMMMYYY	Yes	Yes	Yes	DDMMMYYY	DDMMMYYY	DDMMMYYY
XXXXXX	No		X.X	DDMMMYYY	No	No	Yes	DDMMMYYY	DDMMMYYY	DDMMMYYY
XXXXXX	No		X.X	DDMMMYYY	No	No	Yes	DDMMMYYY	DDMMMYYY	DDMMMYYY
XXXXXX	Yes	XXXXXXX	X.X	DDMMMYYY	Yes	Yes	Yes	DDMMMYYY	DDMMMYYY	DDMMMYYY

Abbreviations: ICF = informed consent form; OLE =open label extension; PK = pharmacokinetic.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period.

Listing 16.2.4.3
Medical History
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXXX

Subject ID	System Organ Class/ Preferred Term/ Verbatim Term	Start Date (Study Day)/ End Date (Study Day)/
XXXXXX	XXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXX	DDMMMYYYY (X)/ DDMMMYYYY (X)
	XXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXX	--MMMYYYY/ Ongoing
	XXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXX	DDMMMYYYY (X)/ Ongoing
XXXXXX	XXXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXXX	DDMMMYYYY (X)/ DDMMMYYYY (X)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. Medical history was coded using MedDRA version 21.1. Only subjects with any medical history recorded are listed.

Programming note: *SOC & PT text should be in title case in table.*

Listing 16.2.5.1
Initial Study Drug Application
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXXX

Subject ID	Was Study Drug Applied?	Date of Application (Study Day)	Time of Administration	Tube Weight Before Drug Application (grams)	Tube Weight After Drug Application (grams)	Amount Used (grams)
XXXXXX	XXX	DDMMMYYYY (X)	HH:MM (X)	XXX	XXX	XXX
XXXXXX	XX; XXXXX					
XXXXXX	XXX	DDMMMYYYY (X)	HH:MM (X)	XXX	XXX	XXX

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming Note: *If drug was not applied, concatenate reason in cell with a semicolon.*

Listing 16.2.5.2
Drug Accountability (Dispensed and Returned)
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXXX

Subject ID	Study Visit	Was Study Drug Dispensed at this Visit?	Dispensation Date (Study Day)	Tube Weight of Tubes Dispensed (grams)	Kit ID Dispensed	Was Study Drug Returned at this Visit?	Return Date (Study Day)	Number of Tubes Returned	Number of Tubes Returned Unused	Tube Weight of Tubes Returned (grams)	Kits Returned
XXXXXX	XXXXXX	XXX	DDMMMYYYY (X)	XXX	XXX	XXX	DDMMMYYYY (X)	XXX	XXX	XXX	XXX
XXXXXX	XXXXXX	XX; XXXXX				XX; XXXXX					
XXXXXX	XXXXXX	XXX	DDMMMYYYY (X)	XXX	XXX	XXX	DDMMMYYYY (X)	XXX	XXX	XXX	XXX

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming Note: *If drug was not dispensed/returned at a visit, concatenate reason in cell with a semicolon.*

Listing 16.2.5.3
Subject Diary
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXXX

Subject ID	Study Visit	Was Diary Data Collected at this Visit?	Dose Number	Date of Dose (Study Day)	Day of the Week	Time Drug Taken	Areas of Skin Treated	Areas Not Treated	Reasons	Cream Reaction
XXXXXX	XXXXXX	XXX	XX	DDMMMYYYY (X)	XXXXXXXX	HH:MM	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
								XXXXXXXX	XXXXXXXX	XXXXXXXX
XXXXXX	XXXXXX	XX; XXXXX								
XXXXXX	XXXXXX	XXX	XX	DDMMMYYYY (X)	XXXXXX	HH:MM	XXXXXXXX	XXXXXXXX	XXXXXXXX	XXXXXXXX
								XXXXXXXX	XXXXXXXX	XXXXXXXX
								XXXXXXXX	XXXXXXXX	XXXXXXXX

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming Note: *If diary data was not collected at this visit, concatenate reason in cell with a semicolon. Include all body areas not treated. If body area not treated or reason is other, concatenate specify field in cell with a semicolon.*

Listing 16.2.5.4.1
Pharmacokinetic Sample Collection
PK Population

Randomized Treatment: XXXXXXXXXXXXXXXX

Subject ID	Was the Sample Collected?	Reason	Date Collected (Study Day)
XXXXXX	XXXXXXX	XXXXXXX	DDMMMYYYY (X)
	XXXXXXX	XXXXXXX	DDMMMYYYY (X)
	XXXXXXX	XXXXXXX	DDMMMYYYY (X)
	XXXXXXX	XXXXXXX	DDMMMYYYY (X)
XXXXXX	XXXXXXX	XXXXXXX	DDMMMYYYY (X)

Abbreviation: PK = pharmacokinetic.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.5.4.2
Pharmacokinetic Sample Collection (Substudy)
PK Population

Randomized Treatment: XXXXXXXXXXXXXXXX

Subject ID	Initial Study Drug Application?	Date Collected (Study Day)	Time	Timepoints	Sample Collected?	Date/Time Collected (Study Day)
XXXXXX	XXX	DDMMMYYYY (X)	HH:MM	XXXXXXX	XXX	DDMMMYYYY/HH:MM (X)
	XXX	DDMMMYYYY (X)	HH:MM	XXXXXXX	XXX	DDMMMYYYY/HH:MM (X)
	XX	DDMMMYYYY (X)	HH:MM	XXXXXXX	XXX	DDMMMYYYY/HH:MM (X)
	XX	DDMMMYYYY (X)	HH:MM	XXXXXXX	XXX	DDMMMYYYY/HH:MM (X)
XXXXXX	XX	DDMMMYYYY (X)	HH:MM	XXXXXXX	XXX	DDMMMYYYY/HH:MM (X)

Abbreviation: PK = pharmacokinetic.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming Note: *If sample was not collected, concatenate reason in cell with a semicolon.*

Listing 16.2.5.4.3
Pharmacokinetic Concentrations
PK Population

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Study Visit	Time In-Clinic Dose Taken	Time Point	Was Sample Collected?	Date/Time Sample Collected (Study Day)	Concentration (unit)
XXXXXX	XXXXXXX	HH:MM	XXXXXXX	Yes	DDMMMYYYY/HH:MM (X)	X.XX
	XXXXXXX	HH:MM	XXXXXXX	Yes	DDMMMYYYY/HH:MM (X)	X.XX
	XXXXXXX	HH:MM	XXXXXXX	Yes	DDMMMYYYY/HH:MM (X)	X.XX
	XXXXXXX	HH:MM	XXXXXXX	No; XXXXXXXX		
XXXXXX	XXXXXXX	HH:MM	XXXXXXX	Yes	DDMMMYYYY/HH:MM (X)	X.XX

Abbreviation: BLQ = below the limit of quantification; PK = pharmacokinetic.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. Any results that are BLQ (i.e., <0.xx) are displayed as BLQ in the listing.

Listing 16.2.5.4.4
Pharmacokinetic Calculated Parameters
PK Population

Randomized Treatment: XXXXXXXXX

Subject ID	AUC_{0-t} (unit)	C_{max} (unit)	T_{max} (unit)	AUC_{0-inf} (unit)	$t_{1/2}$ (unit)	λ_z (unit)
XXXXX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
XXXXX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX

Abbreviation: AUC = area under the plasma concentration-time curve; Cmax = peak plasma concentration; CV = coefficient of variation; λ_Z = apparent terminal phase rate constant. PK = pharmacokinetic; SD = standard deviation; t1/2= first order termination half-life; Tmax = time of Cmax.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. 0-t represents time from 0 to the time of the last quantifiable plasma concentration.

***Programming note**: the number of decimal places depends on the raw data. The above parameters are expected, however the final parameters provided by the pharmacokineticist will be listed.*

Listing 16.2.6.1
Investigator's Global Assessment (IGA)
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Assessment Performed?	Study Visit	Assessment Date (Study Day)	Body Area [1]	Result	Baseline [2]	CFB [3]	% CFB [4]	Successful Resolution of LI?
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	XXXXXX	X	X	X	X	XXX
				XXXXXX	X	X	X	X	XX
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)		X	X	X	X	XXX
					XX	XX	XX	XX	XX
					XX	XX	XX	XX	XXX
					XX	XX	XX	XX	XXX
XXXXXX	XX; XXXXX								

Abbreviations: CFB = change from baseline; IGA = Investigator's Global Assessment; LI = Lamellar Ichthyosis.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. The 5-point (0 - 4) IGA is a measure of disease severity which considers both scaling and roughness. Higher IGA scores represent more severe disease. Successful resolution is defined as clear/almost clear overall and at least a 2-grade change from Baseline on the 5-point (0 - 4) IGA scale.
[1] Body area only for subjects enrolled under protocol version 1.0.
[2] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[3] CFB is calculated as Result – Baseline.
[4] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *If assessment was not performed, concatenate reason with a semicolon. CFB, % CFB and Successful Resolution of LI columns will not be populated for Baseline rows.*

Listing 16.2.6.2
Visual Index for Ichthyosis (VIIS)
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Assessment Performed?	Study Visit	Assessment Date (Study Day)	Body Area	Scaling Score	Baseline [2]	CFB [3]	% CFB [4]
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	Chest/Abdomen	X	X	X	X
				Back	X	X	X	X
				Arms	X	X	X	X
				Legs	XX	XX	XX	XX
				Total	XX	XX	XX	XX
XXXXXX	XX; XXXXX							

Abbreviations: CFB = change from baseline; VIIS = .Visual Index for Ichthyosis.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. The VIIS is scored on a 5-point (0 - 4) scale by body area (chest/abdomen, back, legs, and arms). Higher VIIS scores represent worse scaling.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[2] CFB is calculated as Result – Baseline.
[3] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *If assessment was not performed, concatenate reason with a semicolon. CFB and % CFB columns will not be populated for Baseline rows.*

Listing 16.2.6.3
Roughness Assessment
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Assessment Performed?	Study Visit	Assessment Date (Study Day)	Overall Score for Roughness	Baseline [2]	CFB [3]	% CFB [4]	2-grade CFB?
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	X	X	X	X	XXX
				X	X	X	X	XX
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	X	X	X	X	XXX
				XX	XX	XX	XX	XX
				XX	XX	XX	XX	XXX
				XX	XX	XX	XX	XXX
XXXXXX	XX; XXXXX							

Abbreviations: CFB = change from baseline.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. The individual score for roughness measures the amount of roughness of the skin overall and is scored on a 5-point (0 - 4) scale. Higher scores indicate more severe roughness.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[2] CFB is calculated as Result – Baseline.
[3] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *If assessment was not performed, concatenate reason with a semicolon. CFB and % CFB columns will not be populated for Baseline rows.*

Listing 16.2.6.4
Palm/Sole Assessment
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Assessment Performed?	Study Visit	Assessment Date (Study Day)	Body Area	Assessment	Baseline [2]	CFB [3]	% CFB [4]
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	Palms	X	X	X	X
				Soles	X	X	X	X
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	Palms	XX	XX	XX	XX
				Soles	XX	XX	XX	XX
XXXXXX	XX; XXXXX							

Abbreviations: CFB = change from baseline.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. Thickening of the skin on the palms and soles will be measured on a 5-point (0 - 4) scale. Higher scores indicate more severe thickening.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[2] CFB is calculated as Result – Baseline.
[3] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *If assessment was not performed, concatenate reason with a semicolon. CFB and % CFB columns will not be populated for Baseline rows.*

Listing 16.2.6.5.1
Quality of Life per Dermatology Life Quality Index (DLQI)
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Assessment Performed?	Study Visit	Assessment Date (Study Day)	Item	Score	Baseline [2]	CFB [3]	% CFB [4]
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	1. Over the last week, how itchy, sore, painful or stinging has your skin been?	X	X	X	X
				2. Over the last week, how embarrassed or self conscious have you been because of your skin?	X	X	X	X
				…				
				10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	XX	XX	XX	XX
				Total Score	XX	XX	XX	XX
XXXXXX	XX; XXXXX							

Abbreviations: CFB = change from baseline; DLQI = Quality of Life per Dermatology Life Quality Index.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. DLQI total score is derived as the sum of the 10 individual item scores, with a range of 0 to 30. Higher scores indicate poorer quality of life.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[2] CFB is calculated as Result – Baseline.
[3] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *If assessment was not performed, concatenate reason with a semicolon. CFB and % CFB columns will not be populated for Baseline rows.*

Listing 16.2.6.5.2
Quality of Life per Children's Dermatology Life Quality Index (cDLQI)
All Subjects

Same shell as Listing 16.2.6.5.1

Programming note: *If update to cDLQI throughout footnotes and abbreviations.*

Listing 16.2.6.6
Fissuring Assessment
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Assessment Performed?	Study Visit	Assessment Date (Study Day)	Fissures Present on Palms or Soles?	Body Area	Number of Fissures	Fissure Pain Level
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	XXX	Palms	XX	XXXXX
					Soles	XX	XXXXX
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	XXX	Palms	XX	XXXXXXXX
					Soles	XX	XXXX
XXXXXX	XX; XXXXX						

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming note: *If assessment was not performed, concatenate reason with a semicolon.*

Listing 16.2.6.7
Ectropion Score
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Assessment Performed?	Study Visit	Assessment Date (Study Day)	Item	Score	Baseline [2]	CFB [3]	% CFB [4]
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	Lateral apposition	XX	XX	XX	XX
				Medial apposition	XX	XX	XX	XX
				Scleral show	XX	XX	XX	XX
				Conjunctival show	XX	XX	XX	XX
				Excess tear film	XX	XX	XX	XX
				Redness of the eye	XX	XX	XX	XX
				Round canthus	XX	XX	XX	XX
				Punctum lacrimate	XX	XX	XX	XX
				Total Score	XX	XX	XX	XX

Abbreviations: CFB = change from baseline.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. Ectropion total score is derived as the sum of the 8 individual item scores (lateral apposition, medial apposition, scleral show, conjunctival show, excess tear film, redness of the eye, round canthus, punctum lacrimale), with a range of 0 to 8. Each individual item is scored 0 (nonaffected/no/invisible), 0.5 (<= 1 mm/emerging), or 1 (affected/yes/visible). Higher scores indicates worse ectropion.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[2] CFB is calculated as Result – Baseline.
[3] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *If assessment was not performed, concatenate reason with a semicolon. CFB and % CFB columns will not be populated for Baseline rows.*

Listing 16.2.6.8
EQ-5D
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Assessment Performed?	Study Visit	Assessment Date (Study Day)	Item	Score	Baseline [2]	CFB [3]	% CFB [4]
XXXXXX	XXX	XXXXXX	DDMMMYYYY (XX)	Mobility	XX	XX	XX	XX
				Self-care	XX	XX	XX	XX
				Usual Activities	XX	XX	XX	XX
				Pain/Discomfort	XX	XX	XX	XX
				Anxiety Depression	XX	XX	XX	XX
				Your Health Today	XX	XX	XX	XX
XXXXXX	XX; XXXXX							

Abbreviations: CFB = change from baseline; VAS = visual analog scale.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. The EQ-5D is a measure of health related quality of life. The EQ-5D consists of a descriptive system and the EQ visual analog scale (VAS). The EQ-5D-5L is intended for use in adult subjects. 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.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[2] CFB is calculated as Result – Baseline.
[3] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *If assessment was not performed, concatenate reason with a semicolon. CFB and % CFB columns will not be populated for Baseline rows.*

Listing 16.2.7.1
Adverse Events
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	TEAE? [1]	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/Time (Study Day)/ End Date/Time (Study Day)	Severity/ Relationship to Study Drug	Outcome	Serious?/ Criteria Met	Action Taken/ Other Action Taken?
XXXXX	XXX	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX XXXXXXXXXXXXX	DDMMMYYYY/HH:MM (X)/ DDMMMYYYY/HH:MM (X)	XXXXXXXXX/ XXXXXXXXXX	XXXXXXXXX	XX	XXXXXXXXX/ XXXXXXXXX
XXXXX	XX	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX XXXXXXXXXXXXX	DDMMMYYYY/HH:MM (X)/ DDMONYYYY/HH:MM (X)	XXXXXXXXX/ XXXXXXXXXX	XXXXXXXXX	XX	XXXXXXXXX/ XXXXXXXXX
	XXX	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX XXXXXXXXXXXXX	DDMMMYYYY/HH:MM (X)/ Ongoing	XXXXXXXXX/ XXXXXXXXXX	XXXXXXXXX/	XXX/ XXXXXXXXX	XXXXXXXXX/ XXXXXXXXX

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. AEs were coded using MedDRA version 21.1.
[1] A TEAE is any AE with an onset at the time of or following the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. This will include any AE starting prior to the start of treatment but increasing in severity or relationship at the time of, or following, the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first.

Programming note: *If time missing, display "- -:- -". If Serious? is Yes, concatenate all serious criteria marked as Yes with a semicolon. If no events meet the criteria for display, present "No events are reported." SOC & PT text should be in proper case in table.*

Listing 16.2.8.1
Laboratory Data: Clinical Chemistry
All Subjects

Randomized Treatment: XXXXXXXXXXX

Subject ID	Parameter (unit)	Study Visit	Date/Time of Assessment (Study Day)	Standard Results	Standard Reference Range [1]	Standard Reference Range Flag	CFB [2]	%CFB [3]	Accession Number	Comments
XXXXX	Albumin (unit)	XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XX – YY				XXXXXXX	
		XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XX – YY	XXX	XXX	XXX	XXXXXXX	
		XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XX – YY		XXX	XXX	XXXXXXX	
		XXXXXX		ND						XXXXXXX
		XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XX – YY		XXX	XXX	XXXXXXX	

Abbreviations: AE = adverse event; AL = abnormal-low; AH = abnormal-high; CFB = change from baseline; CS = clinically significant; NCS = not clinically significant; ND = not done.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.
[1] Reference range is used to identify potentially clinically significant laboratory values.
[2] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[2] CFB is calculated as Result – Baseline.
[3] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *update abbreviations to reflect actual data. If test was not done, set results to ND. For reference range flag, concatenate AL or AH with clinical significant like "XX-YY" (e.g., AL-CS). CFB and %CFB columns will be blank for Baseline. Include all parameters.*

Listing 16.2.8.2
Laboratory Data: Hematology
All Subjects

Same shell as Listing 16.2.8.1

Listing 16.2.8.3
Laboratory Data: Coagulation
All Subjects

Same shell as Listing 16.2.8.1

Listing 16.2.8.4
Laboratory Data: Urinalysis
All Subjects

Same shell as Listing 16.2.8.1

Listing 16.2.8.5
Laboratory Data: Serology
All Subjects

Same shell as Listing 16.2.8.1

Listing 16.2.8.6
Laboratory Data: Pregnancy Tests
All Subjects

Randomized Treatment: XXXXXXXXXXX

Subject ID	Sample Type	Was Sample for Urine/Serum Pregnancy Test Collected?	Date of Collection (Study Day)	Result
XXXXX	XXXXXX	XXX	DDMMMYYYY (X)	XXXXXXX
XXXXX	XXXXXX	XXX	DDMMMYYYY (X)	XXXXXXX
XXXXX	XXXXXX	XX; XXXXX		

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming note: *If sample not collected, concatenate reason in cell with a semicolon.*

Listing 16.2.9.1
Vital Signs
All Subjects

Randomized Treatment: XXXXXXXXXXX

Subject ID	Parameter (unit)	Study Visit	Date/Time Collected (Study Day)	Result	CFB [2]	%CFB [3]
XXXXX	Pulse (bpm)	XXXXXX	DDMMMYYYY/ HH:MM (X)	XX		
		XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XXX	XXX
		XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XXX	XXX
XXXXX	XXXXXX	XXXXXX	DDMMMYYYY/ HH:MM (X)	XX	XXX	XXX

Abbreviations: CFB = change from baseline.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[2] CFB is calculated as Result – Baseline.
[3] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *CFB and %CFB columns will be blank for Baseline. Include all parameters.*

Listing 16.2.9.2
12-Lead Electrocardiogram
All Subjects

Randomized Treatment: XXXXXXXXXXX

Subject ID	Parameter (unit)	Study Visit	Timepoint	Was ECG Performed at this Time point?	Date/Time Collected (Study Day)	Result	CFB [2]	%CFB [3]
XXXXX	Pulse (bpm)	XXXXXX	XXXXXX	XX	DDMMMYYYY/ HH:MM (X)	XX		
		XXXXXX	XXXXXX	XX	DDMMMYYYY/ HH:MM (X)	XX	XXX	XXX
		XXXXXX	XXXXXX	XX	DDMMMYYYY/ HH:MM (X)	XX	XXX	XXX
XXXXX	XXXXXX	XXXXXX	XXXXXX	XX	DDMMMYYYY/ HH:MM (X)	XX	XXX	XXX

Abbreviations: CFB = change from baseline; ECG= electrocardiogram.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.
[1] Baseline is defined as the last non-missing assessment recorded prior to the first dose of treatment in the Double-blind Period.
[2] CFB is calculated as Result – Baseline.
[3] % CFB is calculated as Change from baseline / Result at baseline * 100.

Programming note: *If ECG was not performed, concatenate reason in cell with a semicolon.*

Listing 16.2.9.3
Local Tolerability Assessments
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Assessment Collected?	Study Visit	Date Assessment Collected (Study Day)	Body Area	Assessment	Score
XXXXXX	XXX	XXXXXXXX	DDMMMYYYY (X)	Face/Neck	Erythema	XXXXX
					Stinging/Burning	XXXXX
					Pruritus	XXXXX
				XXXXX	XXXXXXXXX	XXXXX
				XXXXX	XXXXXXXXX	XXXXX

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming note: *If assessment was not collected, concatenate reason in cell with a semicolon.*

Listing 16.2.9.4
Physical Examination
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Was Exam Performed?	Study Visit	Exam Date (Study Day)	Body System	Result	Abnormal Findings	Clinically Significant?
XXXXXX	XXX	XXXXXXX	DDMMMYYYY (-X)	General Appearance	Normal		
				Integumentary	Abnormal	XXXXXXXX	No
				Head, Ears, Eyes, Nose, Throat	Normal		

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Programming note: *if physical examination was not performed, concatenate reason with a semicolon.*

Listing 16.2.9.5
Prior and Concomitant Medications
All Subjects

Randomized Treatment: XXXXXXXXXXXXXX

Subject ID	Prior/ Concomitant [1]	Indication	ATC Class (Level 4)/ Preferred Term (ATC Level 5)/ Verbatim Term	Start Date/Time (Study Day)/ End Date/Time (Study Day)	Dose (unit)	Route/ Frequency
XXXXXX	Prior	XXXXXXX	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXX/ XXXXXXXXXXXXX	DDMMMYYYY/hh:mm (X)/ DDMMMYYYY/hh:mm (X)	XXX (XXX)	XXXXXXXX/ XXXXXXX
	Both	XXXXXXX	XXXXXXXXX/ XXXXXXXXXXXXXXX/ XXXXXXXXXXX	--MMMYYYY/--:-- (X)/ Ongoing	XXX (XXX)	XXXXXXXX/ XXXXXXX
	Concomitant	XXXXXXX	XXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXX	DDMMMYYYY/hh:mm (X)/ DDMMMYYYY/hh:mm (XX)	XXX (XXX)	XXXXXXXX/ XXXXXXX

Abbreviations: ATC = anatomic therapeutic chemical; NA = not applicable; WHO-DDE = World Health Organization-Drug Dictionary Enhanced.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug. Medications were coded using WHO-DDE version March 2019.
[1] "Prior" medications are all medications that were started before the first dose of study medication. "Concomitant" medications are medications continuing or starting after the first dose through the end of study. "Both" indicates medication that was started before the first dose and continued during the study.

Programming note: *If Dose unit, Route or Frequency is Other, display other specify text only (i.e., do not display "Other: XXXXXX" but just "XXXXXX "). Sort by subject, start date/time, end date/time, ATC level 4 & PT. ATC & PT text should be in title case in table, as shown in the shell. Ensure proper WHO-DDE version is printed in footnote.*

Listing 16.2.9.6
Photography
All Subjects

Randomized Treatment: XXXXXXXXXXXXXX

Subject ID	Was Photography Collected?	Collection Date (Study Day)
XXXXXX	XXX	DDMMMYYYY (XX)
XXXXXX	XXX	DDMMMYYYY (XX)
XXXXXX	XXX	DDMMMYYYY (XX)
XXXXXX	XXX	DDMMMYYYY (XX)
XXXXXX	XX	
XXXXXX	XXX	DDMMMYYYY (XX)

Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.9.7
Trial Continuation
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Study Visit	Continuing to Next Visit?	Continuing with Drug Administration?	Continuing to OLE?
XXXXXX	XXXXXX	XXX	XXX	XXX
XXXXXX	XXXXXX	XXX	XXX	XXX
XXXXXX	XXXXXX	XXX	XXX	XXX
XXXXXX	XXXXXX	XXX	XXX	XXX
XXXXXX	XXXXXX	XX	XX	XX
XXXXXX	XXXXXX	XXX	XXX	XXX

Abbreviation: OLE = open label extension.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period.

Listing 16.2.9.8
Telephone Contact
All Subjects

Randomized Treatment: XXXXXXXXXXXXXXX

Subject ID	Study Visit	Contacted to Assess New AEs/SAEs?	Contact Date (Study Day)	Report Any New or Worsening AEs/SAEs?	Report Any New Concomitant Medications?
XXXXXX	XXXXXX	XXX	DDMMMYYYY (XX)	XXX	XXX
XXXXXX	XXXXXX	XXX	DDMMMYYYY (XX)	XXX	XXX
XXXXXX	XXXXXX	XXX	DDMMMYYYY (XX)	XXX	XXX
XXXXXX	XXXXXX	XXX	DDMMMYYYY (XX)	XXX	XXX
XXXXXX	XXXXXX	XX; XXXXX			
XXXXXX	XXXXXX	XXX	DDMMMYYYY (XX)	XXX	XXX

Abbreviation: AE = adverse event; OLE = open label extension; SAE = serious adverse event.
Note: Subjects were randomized to either Trifarotene cream HE1 100 ug/g, Trifarotene cream HE1 200 ug/g, or vehicle in the double-blind period. All subjects received Trifarotene cream HE1 200 ug/g in the open label extension period. Study day is calculated relative to the date of first dose of study drug.

Listing 16.2.9.9
COVID-19 Impact Log
All Subjects

Programming Note: *The structure of this listing will be determined prior to database lock, when the log is finalized.*

14.4. Planned Figure Shells

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse events special interest
AIC	Akaike information criterion
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BLQ	beneath limit of quantification
BMI	body mass index
BP	Blood pressure
bpm	Beats per minute
CFB	Change from baseline
CFR	code of federal regulations
CI	confidence intervals
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report
DBP	diastolic blood pressure
DEA	drug enforcement administration
DIA	drug information association
DOB	date of birth

Abbreviation	Definition
EC	ethics committee
ECG	electrocardiogram
EMA	European medicines agency
EOS	End of study
ET	Early termination
FAS	Full analysis set
FDA	food and drug administration
FOCP	Females of childbearing potential
FPC	Follow-up phone call
HR	heart rate
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
ID	identification
IND	investigational new drug
IRB	institutional review board
LS	Least squares
MAR	Missing at random
MedDRA	medical dictionary for regulatory activities
mg	milligram
MI	Multiple imputation
MI	Metacognitive index

Abbreviation	Definition
MMRM	mixed effect model repeat measurement
MNAR	Missing not at random
ms	millisecond
N	number
NA	not applicable
NCS	non-clinically significant
OLE	Open-label extension
PD	protocol deviation
PE	physical examination
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
POC	Point of care
PP	per-protocol
QD	Once daily
QOL	quality of life
REML	Restricted maximum likelihood
RR	respiratory rate or relative rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure

Abbreviation	Definition
SD	standard deviation
SDQ	Symptoms of Depression Questionnaire
SF	screen failure
SM	Study medication
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
USA	United States of America
UTC	universal coordinated time
WHO	world health organization
WHO-DDE	world health organization drug dictionary enhanced