TITLE PAGE

Protocol Title: A Randomized, Parallel, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Two Concentrations of Topical TMB-001 for the Treatment of Congenital Ichthyosis

Protocol Number: 235-9051-202

Amendment Number: 1

Product: TMB-001 (previously PAT-001) (Isotretinoin) Ointment (0.05% and 0.1%)

Short Title: A Vehicle-Controlled Study to Evaluate Safety and Efficacy of Topical TMB-001 for Treatment of Congenital Ichthyosis

Study Phase: 2b

Sponsor Name: Timber Pharmaceuticals, LLC

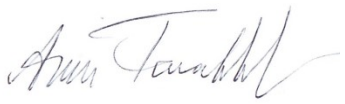
Legal Registered Address: 50 Tice Boulevard, Suite A26, Woodcliff Lake, NJ 07677

Investigational New Drug (IND) number: 122,058

Date of Protocol: 05 Aug 2020

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:



Aug 5, 2020

Amir Tavakkol, PhD, Dip. Bact
Chief Scientific Officer

Date

The Medical Monitor's name and contact information can be found in Appendix 2.

The Investigator's Agreement Page is provided in Appendix 8.

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1.1 Synopsis

Protocol Title: A Randomized, Parallel, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Two Concentrations of Topical TMB-001 for the Treatment of Congenital Ichthyosis

Short Title: A Vehicle-Controlled Study to Evaluate Safety and Efficacy of Topical TMB-001 for Treatment of Congenital Ichthyosis

Rationale:

Timber Pharmaceuticals, LLC, is developing a topical ointment (0.05% and 0.1%) formulation of isotretinoin called TMB-001 (previously PAT-001) (isotretinoin) ointment for the treatment of congenital ichthyosis (CI), including recessive X-linked ichthyosis (RXLI) and autosomal recessive congenital ichthyosis-lamellar ichthyosis (ARCI-LI) subtypes. The purpose of this study is to investigate the efficacy and safety of two concentrations of topically applied TMB-001 in subjects 9 years of age and older.

Objectives and Endpoints

Objectives	**Endpoints**
Efficacy	Primary Efficacy
• To investigate the efficacy of two concentrations of topically applied TMB-001 as a treatment for congenital ichthyosis (CI) of either the autosomal recessive congenital ichthyosis-lamellar ichthyosis (ARCI-LI) or RXLI subtypes.	Proportion of subjects with Visual Index for Ichthyosis Severity - "treatment success" (VIIS-50), which is defined as a 50% or greater decrease in VIIS scaling score relative to Baseline at Visit 6 (EOS) calculated using the sum of the scores for 'VIIS body areas' that have a Baseline score ≥ 3.
	Key Secondary Efficacy
	• IGA scores, dichotomized to "treatment success" or "treatment failure" where "treatment success" is defined as at least a 2-grade decrease in severity score relative to Baseline at Visit 6 (EOS).
	Other Secondary Efficacy
	• Time to achieve VIIS-50 (≥ 50% reduction in VIIS scaling score for body sites that had a Baseline score ≥ 3) that is maintained at the next observation. • Changes in VIIS scaling score relative to Baseline at Visit 4 and Visit 5. • Proportion of subjects with IGA "treatment success" at Visit 4, Visit 5, and Visit 6 (EOS). • Proportion of subjects with an IGA score of 0 or 1 representing "cleared" or "almost cleared" at Visit 6 (EOS). • Changes in percent BSA relative to Baseline with CI in the Treatment/Assessment Areas at Visit 3, Visit 4, Visit 5, and Visit 6 (EOS). • Change from Baseline in Itch-Numeric Rating Scale (I-NRS) score at Visit 6 (EOS). • Proportion of subjects with I-NRS "treatment success" where "success" is defined as at least a

Objectives	Endpoints
	4-point reduction in I-NRS relative to Baseline at Visit 6 (EOS). • Change in DLQI from Baseline to Visit 6 (EOS).
Safety	Safety
• To investigate the safety of topically applied TMB-001.	• Incidence (severity and causality) of any local and systemic AEs. • Number of subjects with presence (and severity) at each time point of the LSRs including burning/stinging, erythema, erosions, and edema. • Changes from Baseline in vital signs at Visit 6 (EOS). • Changes from Baseline in clinical laboratory test results (chemistry, hematology, and urinalysis) at Visit 6 (EOS).

Abbreviations: AE = adverse event; ARCI-LI = autosomal recessive congenital ichthyosis-lamellar ichthyosis; BSA = body surface area; CI = congenital ichthyosis; DLQI = Dermatology Life Quality Index; EOS = End of Study; IGA = Investigator's Global Assessment; I-NRS = Itch-Numeric Rating Scale; LSR = local skin reaction; RXLI = recessive X-linked ichthyosis; VIIS = Visual Index for Ichthyosis Severity.

Overall Design:

This is a randomized, parallel, double-blind, vehicle-controlled study to evaluate the safety and efficacy of two concentrations of topical TMB-001 for the treatment of CI in subjects with either the ARCI-LI or RXLI subtypes. The duration of treatment will be 12 weeks. Each subject will participate in the study for up to 24 weeks (including up to a 90-day Screening period).

Number of Investigators and Study Centers:

Approximately 10 study centers from United States of America and Australia are expected to participate in this global study.

Number of Subjects:

Approximately 45 subjects will be enrolled (15 per treatment arm).

Treatment Groups and Duration:

Each subject will participate in the study for up to 24 weeks (including up to a 90-day Screening period).

Eligible subjects will be randomized (1:1:1) to one of 3 treatment groups:

1. TMB-001, 0.05%, twice daily (bid)
2. TMB-001, 0.1%, bid
3. Vehicle Ointment (Control), 0%, bid

Temporary Discontinuation (Drug Interruption/Holiday)

A treatment interruption scheme will be allowed if a subject experiences skin adverse events or local skin reactions (LSRs) during the study that may require interruption or termination of study medication. This is intended to assist subjects to continue in the study if the event is likely or expected to lead to discontinuation. Any subjects with a local AE (especially early during treatment) will be encouraged to continue with their study medication since transient skin irritation is known to develop with topical retinoids, but AEs may also develop due to the vehicle formulation or otherwise.

It is desirable to make every effort to maintain subjects in the study to allow adequate assessment of efficacy and safety, especially in this small dose ranging study. If during the Treatment Phase there is for example a persistent Grade 2 or greater burning/stinging, erythema, erosions, edema or pruritus, treatment will be

temporarily interrupted (maximum of 2 weeks), and unscheduled visits/phone calls will be scheduled to monitor resolution. As soon as the LSR(s) have resolved, treatment will be restarted at a frequency of once daily for 2 weeks. If treatment is tolerated at this frequency, then treatment will be increased to twice daily or as per protocol. If necessary, a second drug interruption will be allowed according to the instructions above, as per the Investigator's discussion and agreement with the Medical Monitor. For details see section 6.5 and 7.4

Treatment will be permanently discontinued if any of the following occurs:

- If the LSR(s) do(es) not resolve with the interruption of therapy for 2 weeks, or
- If the LSR(s) recur(s) during bid dosing, or
- If a third drug interruption is needed.

Treatment/Assessment Areas:

Treatment/Assessment Areas are defined as:

Treatment area- the area of the entire body with active CI where the study medication will be applied (the entire body except for the hands, face, neck, scalp and genitalia are possible treatment areas.)

Assessment Area- For the purposes of assessing via the Visual Index for Ichthyosis Severity (VIIS)

Four VIIS Assessment Areas within the Treatment Area will be defined as described below and will be further described using color illustrations in the Investigator Study Binder:

(*a*) the upper back from the posterior axillary fold to the other encompassing the T1-T10

(*b*) the upper arm (excluding elbows), left or right

(*c*) the shin/lower leg (the portion below the proximal aspect of the knee cap), left or right

(*d*) dorsal foot (left or right).

The Investigator will include subjects when any of the 4 VIIS Assessment Areas have some CI disease. At least, 2 of the 4 VIIS Assessment Areas MUST have a scaling score of 3 or more. Since for (*b*), (*c*), and (*d*) each include two body parts, one of each left or right must be designated as the Target (upper arm, lower leg, or dorsal foot) and followed throughout the study for VIIS assessment. The arm, leg, or foot with more severe and higher score will be designated as the Target unless they have the same severity scores, in which case the left or right choice will be at the discretion of Investigator assuming no other issues exists, dictating the choice of left/right. The severity scores will be averaged by the electronic data capture system but the score of two body parts that have a score of 3 or higher will be used to enroll subjects and used in subsequent assessments. A five-point (0-4) scale will be used with increasing clinical severity (scaling) and will be defined in the training manual.

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Assessment Area- For the purposes of assessing via the Investigator's Global Assessment (IGA): IGA will be performed on the entire Treatment Area. The IGA assessment by definition will include the VIIS Assessment Area but it will provide a broader perspective on disease status and therapeutic response at baseline and subsequent visits. The IGA score is a static evaluation of the overall or "average" degree of severity of a subject's disease, considering all the subject's scaling and fissuring in the IGA Assessment Areas by the Investigator or designee. This evaluation takes into consideration the 2 individual characteristics of CI (scaling and fissuring) with the IGA score at each visit representing the average degree of scaling and fissuring that is eligible for treatment. The IGA will be assessed using a 5-point scale.

Statistical Methods:

All statistical analyses and summaries will be prepared using SAS® unless otherwise stated. All subjects enrolled in the study who were dispensed and who applied study medication at least once will be included in the analysis of safety and will be considered the Safety population. All randomized subjects, who received at least one dose of study medication will be considered the intent-to-treat (ITT) population. The per-protocol (PP) population will be a subset of the ITT population consisting of subjects who 1) met all inclusion/exclusion criteria that would affect the treatment evaluation, 2) applied ≥ 80% but ≤ 120% of the planned doses of study treatment, 3) who had a VIIS measurement at Visit 6/End of Study (EOS), and 4) had no major protocol violations that would affect the treatment evaluation. The final definition of the PP population will be presented in the Statistical Analysis Plan (SAP).

Efficacy analyses will be performed on both the ITT and PP populations with the ITT population considered primary. Additional analyses may be performed to examine the efficacy in each CI subtype or different age groups which will be described in the SAP prior to data base lock.

Demographic and baseline characteristics will be summarized by treatment group for the Safety, ITT, and PP populations. Frequency counts and percentages will be reported for categorical data and sample size, mean, median, standard deviation (SD), minimum, and maximum will be reported for the continuous variables.

Efficacy Analyses:

VIIS "treatment success" (VIIS-50) is defined as ≥ 50% reduction from Baseline for VIIS scaling score for the sum of the scores for 'VIIS body areas' that had a Baseline score ≥ 3). The proportion of subjects achieving VIIS-50 at Visit 6 (EOS) relative to Baseline will be the primary efficacy endpoint and time point used to compare the two active treatments to vehicle. Treatment groups will be compared at Visit 6 (EOS) using the Cochran-Mantel-Haenszel (CMH) Test stratified by CI subtype and corresponding 95% confidence intervals will be calculated for the difference in proportions for the treatment groups.

The proportion of subjects achieving IGA treatment success will be the key secondary endpoint. For this endpoint, the IGA score will be dichotomized to "treatment success" or "treatment failure" where "treatment success" is defined as at least a 2-grade decrease in severity score relative to Baseline at Visit 6 (EOS).

Additionally, one secondary endpoint is the time to achieve VIIS-50 that is maintained at the next observation. If VIIS-50 is first achieved at Visit 6 (EOS), then the endpoint is considered to have been met. A time to event analysis will be completed using the Kaplan-Meier method and log rank test.

For each of the other secondary efficacy endpoints (VIIS scaling, IGA, and Itch-Numeric Rating Scale [I-NRS]), the following summaries will be prepared at Visits 3, 4, 5, and 6 (EOS) (as applicable) by treatment group for each CI subtype and overall:

- Frequency distribution of observed scores
- Frequency distribution of change from Baseline
- Shift tables for changes from Baseline to Visits 3, 4, 5, and 6
- Frequency distribution of treatment success rates

Success rates between treatment groups will be compared at Visit 6 (EOS) using the CMH Test stratified by CI subtype and 95% confidence intervals will be calculated for the difference in proportions for the treatment groups.

Descriptive statistics (including mean, median, SD, minimum, and maximum) for observed and change from Baseline values in the Dermatology Life Quality Index (DLQI) and percent BSA affected in the Treatment/Assessment Areas at each visit will be presented by treatment group for each CI subtype and overall.

For VIIS and I-NRS, the treatment groups will be compared with respect to the change from Baseline using mixed model of repeated measures (MMRM) including terms for treatment, visit, treatment by visit interaction, and the Baseline value serving as the covariate. From the model, the active to vehicle treatment differences will be estimated. Additionally, two-sided confidence intervals will be provided.

Handling of missing data: Data summaries and analyses will use observed data only without imputation of missing values. Supplementary analysis will be performed to investigate the impact of data imputation on the primary endpoint as follows:

1) by assuming that subjects with missing data are treatment successes ("best case"); and

2) by assuming that subjects in the vehicle group with missing data are "treatment success" and that subjects in the TMB-001 groups with missing data are treatment failures ("worst case").

3) by assuming that subjects with missing data maintain their last observed rating from which treatment success or failure will be derived at Visit 6 ("LOCF").

Dosing Compliance

Descriptive statistics will be used to summarize study treatment compliance for the ITT population. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% but no more than 120% of the expected number of applications or dose.

Safety Analyses:

The safety analyses will be conducted on the Safety population.

Extent of Exposure

The total amount of study medication used (grams of study medication applied) will be calculated from the weights of the returned study medication tubes. Descriptive statistics (mean, median, SD, minimum and maximum) will be determined for the total amount of study medication used by each subject by treatment groups.

Physical Examinations

Findings from physical examinations (head and neck, cardiovascular, dermatological, respiratory, gastrointestinal [abdomen], and gross motor and gait) will be recorded in medical history (from assessment at Visit 1 [Screening] and Visit 2 [Baseline])

Vital Signs

Descriptive statistics of vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) at Visit 1 (Screening) and Visit 6 (EOS) will be provided by treatment group.

Clinical Laboratory Tests

Clinical laboratory tests will be evaluated for any material changes during the study period. All laboratory data (hematology, chemistry, and urinalysis) will be listed and reported in the units received by the laboratory. Shift tables by analyte and by out of range flag will be presented to facilitate the evaluation of change from Visit 1 (Screening) to Visit 6 (EOS).

Urine Pregnancy Test

Urine pregnancy test (UPT) results (if applicable) from Visit 2 (Baseline), Visit 4, Visit 5, and Visit 6 (EOS) will be provided in a listing.

Local Skin Reactions

Local skin reactions (LSRs) (including burning/stinging, erythema, erosions, and edema) will be summarized by frequency of each individual LSR for each treatment group. Change from Baseline in LSRs will be categorized into 'worsened' and 'same or improved' and will be tabulated.

Adverse Events

All AEs reported during the study will be listed, documenting onset, whether therapy was required, any change in study treatment dosing, severity, possible relationship to study treatment, and outcome. Verbatim terms on the case report forms (CRFs) will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to study treatment by treatment group.

Data Monitoring Committee: No

1.2 Schedule of Activities

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening	**Baseline[a]**	**Week 2**	**Week 4**	**Week 8**	**Week 12/EOS[b]**
Days	**-90 to -7**	**1**	**15 (± 4)**	**29 (± 4)**	**57 (± 7)**	**85 (± 7)**
Informed Consent/Assent	X					
Demographics	X					
Inclusion/Exclusion Criteria	X	X[c]				
Medical History	X	X (updated)				
Concomitant Medications and Procedures/Therapies	X	X	X	X	X	X
Genetic testing/confirmation	X					
Physical Examination[d]	X	X (abbreviated)				X (abbreviated)
Vital Signs[e]	X					X
Clinical Laboratory Tests[f]	X					X
Urine Pregnancy Testing[g] for WOCBP[h]		X		X	X	X
Photography (Select Sites and Subjects having remote visits)		X	X	X	X	X
Clinical Evaluations (VIIS and IGA) (select Target for VIIS assessment)	X	Confirm (prior to treatment application)	X	X	X	X
Record percent of BSA with CI in the VIIS Assessment Area and the Treatment Area	X	Confirm	X	X	X	X
Age-appropriate Dermatology Life Quality Index and I-NRS		X			X	X
Local Skin Reactions		X (prior to treatment application)	X	X	X	X
Randomization[i]	X					
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
	Screening	**Baseline[a]**	**Week 2**	**Week 4**	**Week 8**	**Week 12/EOS[b]**

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening	Baseline[a]	Week 2	Week 4	Week 8	Week 12/EOS[b]
Days	-90 to -7	1	15 (± 4)	29 (± 4)	57 (± 7)	85 (± 7)
Days	**-90 to -7**	**1**	**15 (± 2)**	**29 (± 2)**	**57 (± 2)**	**85 (± 3)**
Study Treatment Accountability and dispensation to subject		X	X	X	X	X
Demonstrate how to apply the study treatment[j]		X	X	X	X	
Subject Diary: Dispense (D), Review (R), and/or Collect (C)		D	C+R+D	C+R+D	C+R+D	C+R
Instruct Subject to Continue Daily Treatment		X	X	X	X	
Adverse Events	X	X[k]	X	X	X	X[l]

Abbreviations: AE = adverse event; β-hCG = beta human chorionic gonadotropin; BSA = body surface area; C = collect diary; CI = congenital ichthyosis; D = dispense diary; EOS = End of Study; IGA = Investigator's Global Assessment; I-NRS = Itch-Numeric Rating Scale; R = review diary; VIIS = Visual Index for Ichthyosis Severity; WOCBP = women of childbearing potential.

[a] Screening assessments (except for Genetic testing)may be performed up to 90 days prior to the Baseline Visit for those qualified subjects who are eligible to enroll in the study but require washout of medications prior to enrolling into the Treatment Phase of the study. Genetic confirmation should be obtained prior to conducting additional eligibility assessments in the screening period. There is no window as it pertains to obtaining Genetic confirmation, it can be obtained at any time following consent and with no restriction until the Baseline Visit.

[b] Or early termination from the study.

[c] For those subjects who required genetic testing or a washout period related to exclusionary medications, reaffirm these subjects meet all protocol requirements at the Baseline Visit.

[d] Examination will include head and neck, dermatologic, cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait assessments. Abbreviated examination/ subject disposition via directed query will be conducted at Visit 2 (Baseline) to identify any changes since the Screening Visit and Visit 6 (EOS) to assess changes throughout the study. Abnormalities at Visit 1 (Screening) and Visit 2 (Baseline) will be recorded as medical history. Any new or worsening abnormality at all subsequent visits will be recorded as AEs.

[e] Assessments will be made after the subject has rested in a seated position for at least 5 minutes. Height and weight will also be measured at Visit 1 (Screening).

[f] Clinical laboratory tests (hematology, clinical chemistry, routine urinalysis) are provided in Table 7. Additional screening tests (as mentioned in Table 7) will be performed for Screening. Subjects must be fasting (at least 8 hours) for Visit 1 (Screening) and, if possible, for Visit 6 (EOS). However, if a subject arrives at the clinic for Visit 6 (EOS) without fasting for at least 8 hours, laboratory specimens may be collected as non-fasting, at the discretion of the Investigator and documented as such on the laboratory requisition form.

[g] All urine pregnancy tests must have a minimum sensitivity of 25 mIU β-hCG/mL.

[h] The term WOCBP is defined in Appendix 6.

[i] Subject will be assigned the next available (lowest) kit number in ascending order.

[j] Study staff will provide a Subject Instruction Sheet to the subject and parent/guardian (if applicable).

[k] During any washout and screening periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and was unanticipated. In such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as an "unanticipated problem" in accordance with local procedures.

[l] Any treatment-related AEs that are ongoing at Visit 6 (EOS) must be followed until resolution or stabilization.

2.0 INTRODUCTION

The classification of congenital ichthyosis (CI) is complex because the disorder presents in a multitude of forms and phenotypes. The main features, however, are scaling and often thickening of the skin (1). The presentation and severity of symptoms can differ greatly by patient and by the form of ichthyosis, but generally include skin inflammation and fragility, pruritus, fissuring and cracking of thickened skin, ectropion, anhidrosis, and in some severe cases, an increased susceptibility to infection. Recessive X-linked ichthyosis (RXLI), which occurs at a frequency of about one in 2500 (in males), is clinically characterized by widespread, dark brown, polygonal scales, and generalized dryness (2). The diagnosis can be confirmed using genetic testing to identify a complete deletion of the gene encoding steroid sulfatase (STS) that is located at the terminus of the X chromosome (3). Autosomal recessive congenital ichthyosis-lamellar ichthyosis (ARCI-LI), which occurs at a frequency of about one in 100,000 to 300,000, is a member of the nonsyndromic autosomal recessive CI group which manifests itself clinically as hyperkeratosis and dry, scaling skin across the entire body (4); pathogenesis is related to a severely disturbed barrier function due either abnormal corneocytes or to a defective deposition of stratum corneum lipids and is typically caused by truncation or missense mutations in the gene encoding keratinocyte transglutaminase type 1 (TGM1) (1, 4).

Isotretinoin is a “natural” retinoid (13-cis isomer of naturally occurring tretinoin [all-trans-retinoic acid{RA}]) that was initially developed as a synthetic retinoid, but it is also present in cells as a naturally occurring metabolite (5). Isotretinoin is structurally and pharmacologically related to vitamin A, which regulates epithelial cell growth and differentiation (6). Isotretinoin has several pharmacological mechanisms of action that result in the suppression of sebaceous gland activity, reduction of sebum production, reduction of comedogenesis by decreasing hyperkeratinization, suppression of *Propionibacterium acnes* (*P. acnes*), and reduction of inflammation (7). Isotretinoin has at least 5 biologically important metabolites: 13-*cis*-4-oxo-RA (4-oxo-isotretinoin), all-trans-RA (tretinoin), all-trans-4-oxo-RA (4-oxo-tretinoin), 9-*cis*-RA (alitretinoin), and 9-*cis*-4-oxo-RA; and can be considered a pro-drug, in which isotretinoin can be metabolized into the naturally occurring tretinoin (or one of the other metabolites) as the active intracellular moiety (7). In addition, while some of isotretinoin’s activity may be mediated by tretinoin, the isomerization of isotretinoin (13-cis-RA) into tretinoin (all-trans-RA) does not account for all of the pharmacological effects observed upon use of this retinoid (8). Thus, isotretinoin’s broader range of activity compared to other retinoids makes it advantageous for clinical development.

Oral isotretinoin (Accutane®) capsules was first approved by the United States (US) Food and Drug Administration (FDA) as treatment for severe recalcitrant nodular acne in 1982 (9). Teratogenicity is regarded as one of the most serious potential adverse effects of oral retinoids, while common mucocutaneous side effects are dose-dependent and can be managed by modification of the dose (eg, reductions and/or drug holidays) and additional symptomatic therapy

(eg, moisturizers). Topical formulation of isotretinoin, Isotrex® gel and cream, 0.05%, has since been approved in various countries outside of the US for the treatment of mild to moderate acne vulgaris, characterized by comedones, papules, and pustules (6,10). Another topical formulation, isotretinoin cream, 0.1%, has also been studied in various indications including ichthyosis and other disorders of keratinization (11,12) and acne vulgaris (13, 14, 15, 16, 17).

2.1 Study Rationale

Systemic retinoids, including isotretinoin, have been used for the investigational treatment of CI and have demonstrated remarkable efficacy in reducing the clinical signs of the disease while dosing of the drug is maintained. Although not FDA approved, topical formulations of isotretinoin (eg, 0.05% gel and 0.1% cream) have demonstrated some efficacy in reducing the clinical signs associated with ichthyosis and other disorders of keratinization. Timber Pharmaceuticals, LLC is developing a topical ointment (0.05% and 0.1%) formulation of isotretinoin called TMB-001 (previously PAT-001) (isotretinoin) ointment for the treatment of CI, including RXLI and ARCI-LI subtypes. For ARCI-LI subjects, enrollment is not limited to Transglutaminase 1 mutations. Other genetically confirmed ARCI-LI mutations can potentially be enrolled as long as the phenotype is consistent with ARCI-LI and the other inclusion criteria are met, as determined by the Investigator. The purpose of this study is to investigate the efficacy and safety of two concentrations of topically applied TMB-001 in subjects 9 years of age and older. More recently, a pilot Phase 2a, multicenter study in subjects ≥ 12 years of age showed topically applied TMB-001 ointment (0.1%) to be safe, tolerable, and supporting a favorable efficacy signal with improvement in overall Investigator's Global Assessment (IGA) for CI treatment.

2.2 Background

Congenital ichthyosis is a large, heterogeneous family of inherited skin disorders of cornification resulting from an abnormality of skin keratinization (1).

The management of CI is a life-long endeavor, which remains largely symptomatic (ie, emollients with or without keratolytics) and commonly focused on reducing scaling and/or skin lubrication with both systemic and topical treatments (1). A first-line therapy includes hydration and lubrication accomplished by creams and ointments containing low concentrations of salt, urea, or glycerol, which increases the water-binding capacity of the horny layer. Addition of keratolytics is used to decrease corneocyte cohesiveness, to promote desquamation, and to dissolve keratins and lipids (eg, α-hydroxy acids, salicylic acid, high-dose urea, propylene glycol, *N*-acetylcysteine, and retinoids). Systemic retinoid treatment is reserved for those patients who are refractory to topical agents because of long-term adverse effects and teratogenicity (5); however, the investigational use of oral isotretinoin has demonstrated remarkable efficacy when used for the treatment of ichthyoses and is believed to be attributable to isotretinoin's ability to reduce comedogenesis by decreasing hyperkeratinization (1, 5). For the treatment of CI, it would be desirable to have a topical formulation of isotretinoin as it would afford targeted delivery of the

drug at the disease tissue site, while potentially minimizing systemic exposure compared to that of systemic retinoid treatment, and additionally providing hydration and lubrication to the diseased skin.

2.3 Benefit/Risk Assessment

While no topical isotretinoin formulation is approved for use in treatment of CI (or any indication in the US), topical formulations of isotretinoin (eg, 0.05% gel and 0.1% cream) have demonstrated some efficacy in reducing the clinical signs associated with ichthyosis and other disorders of keratinization. In one study, topical 13-cis-RA (isotretinoin) cream 0.1% demonstrated a marked reduction in scaling and an improvement in skin smoothness after 4 weeks of treatment in 40% of subjects (2/7 patients with non-erythrodermic LI, 2/2 patients with Darier's disease, and 0/1 patients with autosomal dominant ichthyosis vulgaris). However, this clinical improvement was accompanied by local skin irritation (eg, itchy erythema) in responders, and dose modifications were often prescribed to mitigate such effects (12). Similarly, topical isotretinoin gel, 0.05% (Isotrex®) demonstrated partial resolution or clearance of hyperkeratosis and papules in the treatment area (10 cm^2 area) after 3 months of treatment (up to twice daily [bid] as tolerated) in 50% (6/12) of patients with Darier's disease.

In addition, systemic retinoids, including isotretinoin, have been used for the investigational treatment of CI and have demonstrated remarkable efficacy in reducing the clinical signs of the disease while dosing of the drug is maintained (1, 5).

More recently, a pilot Phase 2a, multicenter study in subjects ≥ 12 years of age showed topically applied TMB-001 ointment (0.1%) to be safe, tolerable, and supporting a favorable efficacy signal with improvement in overall IGA for CI treatment.

As with any retinoid, the side effects of TMB-001 may include the following local skin reactions (LSRs): burning, dryness, edema, erythema, hyperpigmentation, hypopigmentation, photosensitivity, pruritus, scaling/peeling, stinging, and tenderness.

Although systemic exposure is expected to be low given the route of topical administration. In minipigs receiving once daily dermal applications of TMB 001 ointment at concentrations of 0% (control), 0.025%, 0.1%, and 0.2%, there was little to no systemic absorption of isotretinoin with most values being near or below the limit of quantitation (0.374 ng/mL).

In addition, in a Phase 2a clinical study of subjects with CI, the concentrations of isotretinoin and tretinoin were measured. Plasma concentrations of isotretinoin and tretinoin indicated that systemic exposure was minimal within the 4 hours following initial application. Trough concentrations measured on Days 8, 29, 57 and 84 approximately 12 hours following the preceding dose indicated that systemic concentrations of isotretinoin and tretinoin were within range of the endogenous levels measured at Baseline prior to the first application.

The most notable adverse reactions with oral isotretinoin are: dry lip, dry skin, back pain, dry eye, arthralgia, epistaxis, headache, nasopharyngitis, chapped lips, dermatitis, renal or hepatotoxicity, musculoskeletal discomfort, teratogenicity, and visual acuity reduced.

The following are concerns for women of childbearing potential (WOCBP):

- Severe birth defects can occur during pregnancy while taking oral isotretinoin, with any amount and even if taken for short periods of time;
- Pregnancy must be avoided 1 month before, during, and for 1 month after treatment.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of TMB-001 ointment may be found in the Investigator's Brochure.

3.0 OBJECTIVES AND ENDPOINTS

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Efficacy	Primary Efficacy
• To investigate the efficacy of two concentrations of topically applied TMB-001 as a treatment for congenital ichthyosis (CI) of either the autosomal recessive congenital ichthyosis-lamellar ichthyosis (ARCI-LI) or RXLI subtypes.	Proportion of subjects with VIIS "treatment success" (VIIS-50), which is defined as a 50% or greater decrease in VIIS scaling score relative to Baseline at Visit 6 (EOS) calculated using the sum of the scores for 'VIIS body areas' that have a Baseline score ≥ 3.
	Key Secondary Efficacy
	• IGA scores, dichotomized to "treatment success" or "treatment failure" where "treatment success" is defined as at least a 2-grade decrease in severity score relative to Baseline at Visit 6 (EOS).
	Other Secondary Efficacy
	• Time to achieve VIIS-50 (≥ 50% reduction in VIIS scaling score for body sites that had a Baseline score ≥ 3) that is maintained at the next observation. • Changes in VIIS scaling score relative to Baseline at Visit 4 and Visit 5. • Proportion of subjects with IGA "treatment success" at Visit 4, Visit 5, and Visit 6 (EOS). • Proportion of subjects with an IGA score of 0 or 1 representing "cleared" or "almost cleared" at Visit 6 (EOS). • Changes in percent BSA relative to Baseline with CI in the Treatment/Assessment Areas at Visit 3, Visit 4, Visit 5, and Visit 6 (EOS). • Change from Baseline in I-NRS score at Visit 6 (EOS). • Proportion of subjects with I-NRS "treatment success" where "success" is defined as at least a 4-point reduction in I-NRS relative to Baseline at Visit 6 (EOS). • Change in DLQI from Baseline to Visit 6 (EOS).

Objectives	**Endpoints**
Safety	Safety
• To investigate the safety of topically applied TMB-001.	• Incidence (severity and causality) of any local and systemic AEs. • Number of subjects with presence (and severity) at each time point of the following LSRs: burning/stinging, erythema, erosions, and edema. • Changes from Baseline in vital signs at Visit 6 (EOS). • Changes from Baseline in clinical laboratory test results (chemistry, hematology, and urinalysis) at Visit 6 (EOS).

Abbreviations: AE = adverse event; ARCI-LI = autosomal recessive congenital ichthyosis-lamellar ichthyosis; BSA = body surface area; CI = congenital ichthyosis; DLQI = Dermatology Life Quality Index; EOS = End of Study; IGA = Investigator's Global Assessment; I-NRS = Itch-Numeric Rating Scale; LSR = local skin reaction; RXLI = recessive X-linked ichthyosis; VIIS = Visual Index for Ichthyosis Severity.

4.0 STUDY DESIGN

4.1 Overall Design

This is a randomized, parallel, double-blind, vehicle-controlled study to evaluate the safety and efficacy of two concentrations of topical TMB-001 for the treatment of CI in subjects with either the ARCI-LI or RXLI subtypes.

Approximately 10 study centers from United States of America and Australia are expected to participate in this global study.

The duration of treatment will be 12 weeks.

Each subject will participate in the study for up to 24 weeks (including up to a 90-day Screening period).

4.1.1 Treatment Groups

Eligible subjects will be randomized (1:1:1) to 1 of 3 treatment groups:

1. TMB-001 Ointment, 0.05%, bid
2. TMB-001 Ointment, 0.1%, bid
3. Vehicle Ointment (Control), 0%, bid

4.1.2 Treatment/Assessment Areas

Treatment/Assessment Areas are defined as:

4.1.2.1 Treatment Area

The area of the entire body with active CI where the study medication will be applied (the entire body except for the hands, face, neck, scalp and genitalia are possible treatment areas.)

4.1.2.2 The Visual Index for Ichthyosis Severity (VIIS) Assessment Areas

The primary efficacy assessment will be performed using the Visual Index for Ichthyosis Severity (VIIS). Four VIIS Assessment Areas will be defined as described below and will be further described using color illustrations in the Investigator Study Binder:

(*a*) the upper back from the posterior axillary fold to the other encompassing the T1-T10,

(*b*) the upper arm (excluding elbow), left or right,

(*c*) the shin/lower leg (the portion below the proximal aspect of the knee cap), left or right

(*d*) dorsal foot (left or right).

The Investigator will include subjects when any of the 4 VIIS Assessment Areas have some CI disease. At least 2 of the 4 VIIS Assessment Areas MUST have a scaling score of 3 or more. Since for (*b*), (*c*), and (*d*) each include two body parts, one of each left or right must be designated as the Target (upper arm, lower leg, or dorsal foot) and followed throughout the study for VIIS assessment. The arm, leg, or foot with more severe and higher score will be designated as the Target unless they have the same severity scores, in which case the left or right choice will be at the discretion of Investigator assuming no other issues exists, dictating the choice of left/right. The severity scores will be averaged by the electronic data capture system but the score of two body parts that have a score of 3 or higher will be used to enroll subjects and used in subsequent assessments. A five-point (0-4) scale will be used with increasing clinical severity (scaling) and will be defined in the training manual.

The primary efficacy endpoint will be the proportion of subjects with VIIS "treatment success" (VIIS-50), which is defined as a 50% or greater decrease in VIIS scaling score relative to Baseline at Visit 6, End of Study (EOS) calculated using **only** the VIIS body areas described above that have a Baseline score ≥ 3.

VIIS severity will be calculated as above via one of two methods below

- On-site visual inspection of the VIIS areas
- Virtual/Remote visit comprised of both photographs and tele-medicine utilizing synchronous video-conferencing technology. The severity score at each visit will be based off information gathered from both sources to yield one score.

4.1.2.3 The Investigator's Global Assessment (IGA) Assessment Area

The IGA will be performed on the entire Treatment Area. The IGA assessment will inherently include the VIIS Area but it will provide a broader perspective on disease status and therapeutic response at baseline and subsequent visits. The IGA score is a static evaluation of the overall or "average" degree of severity of a subject's disease, considering all the subject's scaling and fissuring in the - Treatment Areas by the Investigator or designee. This evaluation takes into consideration the 2 individual characteristics of CI (scaling and fissuring) with the IGA score at each visit representing the average degree of scaling and fissuring that is eligible for treatment. The IGA will be assessed using the 5-point scale as shown in Table 3.
IGA severity will be calculated as above via one of two methods below:

- On-site visual inspection
- Virtual/Remote visit comprised of both photographs and tele-medicine utilizing synchronous video conferencing technology. The severity score at each visit will be based off information gathered from both sources to yield one score.

4.2 Scientific Rationale for Study Design

The proposed study will use a multicenter, randomized, double-blind, parallel group, vehicle-controlled study design to evaluate the efficacy and safety of 0.1% and 0.05% TMB-001 in the treatment of CI. The subjects will be selected according to predefined entry criteria. The study treatment duration is 12 weeks and expected to be enough to show a treatment effect.

Isotretinoin was first approved in the US by the FDA and formulated as an oral product, Accutane (isotretinoin) capsules, to treat severe recalcitrant nodular acne (9). A topical formulation of isotretinoin, Isotrex® (isotretinoin) gel, 0.05%, has been approved in various countries outside of the US for the treatment of mild to moderate inflammatory acne vulgaris (6). The pharmacology, pharmacokinetics, and toxicology of isotretinoin have been well characterized in the literature.

Isotretinoin is an approved active pharmacological ingredient with a long history of safe use in humans under the iPLEDGE program (18). The iPLEDGE program is a risk management distribution program mandated by the FDA for isotretinoin because isotretinoin must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking oral isotretinoin in any amount, even for a short period of time. Potentially any fetus exposed during pregnancy can be affected.

4.3 Justification for Dose

The concentrations of TMB-001 ointment chosen for this study are based on the formulation integrity and Phase 2a clinical study, specific laboratory animal toxicology studies performed by the Sponsor, and a review of the published safety data for isotretinoin. The highest dose (0.2% topically applied ointment) tested in the Phase 2a clinical study was reported with retinoid dermatitis and lower tolerability, hence doses lower than 0.2% have been considered for this study. The doses to be applied, 0.1% and 0.05%, are based upon the potential for therapeutic benefit balanced with the safety risk.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed the last scheduled visit (Visit 6) per the Schedule of Activities (Section 1.2).

The end of the study is defined as the date of the last visit of the last subject in the study globally.

5.0 STUDY POPULATION

The subjects will be male and/or female subjects, 9 years of age and older, with moderate to severe CI genetically confirmed to be of either the ARCI-LI or RXLI subtypes according to protocol-specified definitions.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

To enter the study, a subject must meet the following criteria:

1. Subject is male or female, 9 years of age and older at Visit 2 (Baseline).
2. Subject has provided written informed consent/assent. A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of consent/assent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at that time to continue study participation.
3. Females must be postmenopausal (defined as amenorrhea greater than 12 consecutive months in women 50 years of age and older), surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), or use acceptable forms of birth control. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT) at Visit 2 (Baseline) (UPTs must have a minimum sensitivity to detect 25 mIU beta-human chorionic gonadotropin [β-hCG]/mL). Methods of acceptable contraception are further defined in Appendix 6. Female subjects who become sexually active or begin to have relations with a partner during the study must agree to use 2 forms of birth control for 30 days prior to having relations and to continue such forms for the duration of the study.
4. Subject has clinical diagnosis of CI and has a genetic confirmation of either ARCI-LI (eg, transglutaminase 1-deficient) or RXLI (eg, deletion of steroid sulfatase gene) subtypes of CI. For ARCI-LI subjects, enrollment is not limited to Transglutaminase 1 mutations. Other genetically confirmed ARCI-LI mutations can potentially be enrolled as long as the phenotype is consistent with ARCI-LI and the other inclusion criteria are met, as determined by the Investigator. Congenital Ichthyosis XomeDxSlice will be used to diagnose both RXLI and ARCI-LI. GeneDx tests detect transglutaminase mutations in the TGM1 gene, X-linked recessive steroid sulfatase mutations in the STS gene, and additionally analyzes 47 other genes linked to CI. This is a multi-gene panel testing so that all known causes of CI can be confirmed/ruled-out since there is phenotypic overlap between the subtypes (including STS). The tests are considered Laboratory Developed Tests (LDTs) and are thus regulated per US regulations 42 CFR 493 and the laboratory is accredited by the College of American Pathologists.

5. The amount of CI affected skin in the Treatment Area at Baseline will be between a minimum of 10% and maximum of 90% of the total BSA (1% BSA is approximately equal to the surface area of the subject's palm and fingers, with the fingers extended yet grouped together, creating a flat oval-like surface area).
6. Subject's designated VIIS assessment areas MUST:

   - Include any of the 4 VIIS assessment areas that have some CI disease involving: (*a*) the upper back from the posterior axillary fold to the other encompassing the T1-T10, (*b*) the upper arm (excluding elbows), left or right, (*c*) the shin/lower leg (the portion below the proximal aspect of the knee cap), left or right, and (*d*) dorsal foot (left or right); AND
   - At least 2 of the 4 VIIS assessment areas MUST have a scaling score of 3 or more.

7. Subject and parent/guardian (if applicable) are willing and able to apply the study treatment(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.
8. Subject, in the Investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of the Treatment/Assessment Areas or exposes the subject to an unacceptable risk by study participation.

5.2 Exclusion Criteria

A subject is ineligible to enter the study if he/she meets 1 or more of the following criteria:

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject has inflammatory skin diseases that confound the interpretation of results (eg, atopic dermatitis) unrelated to ichthyosis.
3. Subject has previously failed on topical/oral retinoid therapy for treatment of CI.
4. Subject, in the Treatment/Assessment Areas, has used: (*a*) topical retinoids or any other topical prescription or over-the-counter therapies (except emollients, keratolytics, and topical steroids - see below), that are intended for, or that in the opinion of the Investigator, may improve CI within 2 weeks of Visit 2 (Baseline), or (*b*) keratolytics or topical corticosteroids within 5 days prior to Visit 2 (Baseline).
5. Subject has used any topical products in the Treatment/Assessment Areas, including bland emollients, on Visit 2 (Baseline) prior to randomization.
6. Subject has used ultraviolet (UV) treatment within 4 weeks prior to Visit 2 (Baseline).
7. Subject has undergone systemic therapies using vitamin A supplements or St. John's Wort within 4 weeks prior to Visit 2 (Baseline). Note: Use of a multivitamin including Vitamin A is not exclusionary provided it is taken as directed on the packaging.
8. Subject has used systemic retinoids within 12 weeks of Visit 2 (Baseline) or any other systemic therapies that are intended for or may improve CI within 4 weeks of Visit 2 (Baseline).
9. Subject is immunosuppressed (eg, human immunodeficiency virus, systemic malignancy, graft host disease) or receives systemic immunotherapy.

10. Subject is currently taking concomitant immunosuppressive drugs, including systemic corticosteroids, within 2 weeks of Visit 2 (Baseline).
11. Subject has untreated secondary infections; however, subject may become eligible after successful treatment of his/her infection(s) at the Investigator's discretion.
12. Subject is currently enrolled in an investigational drug or device study or has used an investigational drug or investigational device treatment within 30 days prior to Visit 2 (Baseline).
13. Subject has lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the Treatment/Assessment Areas.
14. Subject has a physical condition or other dermatologic disorder that, in the Investigator's opinion, might impair evaluation of CI, or that exposes the subject to unacceptable risk by study participation.
15. Subjects with ALT or AST > 2 × Upper Limit of Normal (ULN) and creatinine > 1.5 × ULN.
16. Subject is unable to communicate or cooperate with the Investigator due to language problems, impaired cerebral function, or physical limitations.
17. Subject has a history of drug or alcohol abuse within the past 6 months, or if suspected to be noncompliant or is unlikely to comply with the requirements of the study protocol (eg, due to alcoholism, drug dependency, mental incapacity) in the opinion of the Investigator.
18. Subject has a history of sensitivity to any of the ingredients in the study treatments (see Section 6.1).

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Subjects must fast at least 8 hours prior to the collection of specimens for clinical laboratory testing at Visit 1 (Screening) and, if possible, for Visit 6 (EOS). However, if a subject arrives at the clinic for Visit 6 (EOS) without having fasted for at least 8 hours, laboratory specimens may be collected as non-fasting, at the discretion of the Investigator and documented as such on the laboratory requisition form.

5.3.2 Activity

No activity restrictions are applicable.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria, and any serious adverse event (SAE) will be collected and recorded in the electronic data capture system.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

Eligible subjects who are not able to complete all their screening assessments within the designated screening period may be rescreened at the discretion of the Sponsor. Rescreening for other reasons may be allowed after consultation with the Sponsor. All screening assessments except for the ICF/Assent, confirmation of CI diagnosis, height, and buccal swab for DNA will be repeated unless determined otherwise by the Sponsor.

Participants who have a clinically nonsignificant out-of-range laboratory result may be rescreened 1 time only at the discretion of the Investigator and after consultation with the Sponsor. For normal ranges, refer to the Laboratory Manual.

Rescreened subjects should not be assigned the same subject number as for the initial screening.

6.0 STUDY TREATMENT

6.1 Study Treatment(s) Administered

The blinded study treatments to be used in this study include:

- TMB-001, 0.05%, bid
- TMB-001, 0.1%, bid
- Vehicle Ointment (Control) bid

The study medication is intended to be applied twice daily, ideally once in the morning and once in the evening, but at least 6 hours apart.

Subjects are instructed to use the indicated amount of study medication on the VIIS Treatment/Assessment Areas. Refer to the Subject and Site Instruction Sheet for per protocol amounts of medication to be applied based on subject's BSA%.

Product application will be clearly demonstrated by the Investigator or a designated healthcare professional at the Baseline Visit.

The study treatment details are provided in Table 2. The Vehicle ointment contains only the inactive ingredients and color additive so that the active and vehicle formulations are indistinguishable.

The Treatment/Assessment Areas are described in Section 4.1.2.

Table 2 Study Treatments

Study Treatment Name:	**TMB-001 0.05%**	**TMB-001 0.1%**	**Vehicle**
Dosage Formulation:	Ointment	Ointment	Ointment
Unit Dose Strength(s)/Dosage Level(s):	0.05%	0.1%	Not applicable
Route of Administration	Topical	Topical	Topical
Dosing Instructions:	Twice daily (morning and evening)	Twice daily (morning and evening)	Twice daily (morning and evening)
Packaging and Labeling	Study medication will be provided in aluminum tubes. Each aluminum tube will be labeled as required per country requirement.	Study medication will be provided in aluminum tubes. Each aluminum tube will be labeled as required per country requirement.	Vehicle ointment will be provided in aluminum tubes. Each aluminum tube will be labeled as required per country requirement.
Manufacturer	Ferndale Laboratories in Ferndale, Michigan, USA	Ferndale Laboratories in Ferndale, Michigan, USA	Ferndale Laboratories in Ferndale, Michigan, USA

6.2 Preparation/Handling/Storage/Accountability

TMB-001 ointment and Vehicle ointment are manufactured in a current Good Manufacturing Practice (GMP)-compliant facility and tested prior to release to ensure that the quality characteristics of each clinical batch are met. TMB-001 ointment and Vehicle ointment are packaged in aluminum tubes and should be stored at the conditions specified on the label as follows:

- Store at 36°F to 46°F (2°C to 8°C) until dispensed. Once dispensed, store at 68°F to 77°F (20°C to 25°C), excursions permitted to 59°F to 86°F (15°C to 30°C).

For Subjects that will be seen in clinic for Visit 2, study medication will be shipped directly to the study site. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study medications received and any discrepancies are reported and resolved before use of the study medication.

For Subjects that will have Visit 2 performed remotely, the study medication will be shipped directly to the subject's home. The subject will receive confirmation from the courier that appropriate temperature conditions have been maintained during transit for all study medications received and the courier will report any discrepancies to the site. In case of discrepancies the site will ensure they are resolved before use of the study medication and communicate that to the subject.

Prior to using any tube, the tube must be weighed. Upon return of the tube to the study center, the tube must be weighed.

Only subjects enrolled in the study may receive study treatment, and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The Investigator or designee is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records) using the Drug Accountability Form. These forms must be available for inspection at all times.

Further guidance and information for the final disposition of unused study medication are provided in the Investigator Study Binder.

6.3 Measures to Minimize Bias: Randomization and Blinding

Subjects who meet all inclusion criteria and no exclusion criteria will be randomized to a treatment group in a 1:1:1 ratio, stratified by CI subtype.

All subjects will be centrally assigned to randomized study treatment using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each study center.

Study medication use will be accounted and dispensed at the study visits as summarized in the Schedule of Activities (Section 1.2).

In this double-blind study, all personnel involved, ie, physicians, site staff, and participants will remain blinded at all times, except in an emergency, where knowledge of the randomization code is required to provide appropriate treatment. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, every effort should be made to contact the Sponsor and Medical Monitor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic Case Report Form (eCRF), as applicable.

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in Section 7.4. Any departures from the intended regimen must be recorded in the eCRFs.

During the course of the study, compliance to study drug application will be evaluated via Subject diaries and accountability by the site, including weighing the tubes. Subjects exhibiting poor compliance should be counseled on the importance of good compliance to the study dosing regimen.

6.5 Concomitant Therapy

Prohibited medications include the use of the following in the Treatment Areas:

- Topical retinoids or any other topical prescription or over-the-counter therapies that are intended for, or that in the opinion of the Investigator may improve, CI within 2 weeks of Visit 2 (Baseline) and until the Visit 6 (EOS);
- Keratolytics, or topical corticosteroids within 7 days prior to Visit 2 (Baseline) and until the Visit 6 (EOS); and,
- Topical products, at Visit 2 (Baseline) and until the Visit 6 (EOS). Bland emollients and over the counter low potency hydrocortisone (e.g.,1% cream) may only be used in the event of severe discomfort (e.g., burning/erythema/itch) and if it is the opinion of the Investigator that a drug interruption (per section 7.4) alone will not relieve the symptoms and these may

cause the subject to discontinue from study. The duration of the mitigation plan should not exceed 2 weeks.
- Topical antibiotic or antifungal can be used after consultation and at the discretion of the Investigator. Systemic antifungals or antibiotics must be prescribed by the Investigator if necessary to avoid risk of more serious or broader infections.

The following systemic treatments are prohibited:

- Vitamin A supplements or St. John's Wort within 4 weeks prior to Visit 2 (Baseline) and until the Visit 6 (EOS) Note: Use of a multivitamin including Vitamin A is not exclusionary provided it is taken as directed as on the packaging;
- Retinoids within 12 weeks of Visit 2 (Baseline) or any other systemic therapies which are intended for or may improve CI within 4 weeks of Visit 2 (Baseline) and until the Visit 6 (EOS); and,
- Immunosuppressive drugs, including systemic corticosteroids, within 2 weeks of Visit 2 (Baseline) and until the Visit 6 (EOS).

The use of UV light is prohibited within 4 weeks prior to Visit 2 (Baseline) and until the Visit 6 (EOS). Further, subjects should limit exposure to UV via sunlight and avoid tanning beds.

Subjects may not be enrolled in an investigational drug or device study or have used an investigational drug or investigational device treatment within 30 days prior to Visit 2 (Baseline).

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded on the eCRF along with:

- Reason for use;
- Dates of administration including start and end dates; and,
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6 Dose Regimen Modification

Dose regimen modification is not allowed in this study, except for a structured treatment interruption scheme (drug holiday) as detailed in Section 7.4.

6.7 Treatment after the End of the Study

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for subjects with CI.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

See the Schedule of Activities (Section 1.2) for a list of the data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1 Pregnancy

Any female subject who becomes pregnant during the study must discontinue treatment. If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 8.4.5 and Appendix 6.

7.2 Inadvertent Enrollment

If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject must be discontinued from study treatment; and the Sponsor or Sponsor designee must be contacted.

7.3 Adverse Events

A subject may discontinue from the study due to an SAE or AE. In that case, the procedures in Section 8.4 must be followed.

See the Schedule of Activities (Section 1.2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.4 Temporary Discontinuation (Drug Interruption/Holiday)

A treatment interruption scheme will be allowed if a subject experiences skin adverse events or LSRs during the study that may require interruption or termination of study medication. This is intended to assist subjects to continue in the study if the event is likely or expected to lead to discontinuation. Any subjects with a LSR (especially early during treatment) will be encouraged to continue with their study medication since transient skin irritation is known to develop with topical retinoids, but LSRs may also develop due to the vehicle formulation or other reasons.

It is desirable to make every effort to maintain subjects in the study to allow adequate assessment of efficacy and safety, especially in this small dose-ranging study. If during the Treatment Phase there is a persistent Grade 2 or greater adverse event, treatment can be temporarily interrupted, and unscheduled visits/phone calls will be scheduled to monitor resolution. Supportive action (per section 6.5) can be undertaken, if in the opinion of the Investigator the drug interruption alone will not relieve the symptoms and may cause the subject to discontinue from study. As soon as the LSR(s) have resolved, study medication will be restarted at a frequency of once daily for 2 weeks. If treatment is tolerated at this frequency, then treatment will be increased to twice daily or as per protocol. If necessary, a second drug interruption will be allowed according to the instructions above, as per the Investigator's discussion and agreement with the Medical Monitor.

Treatment will be permanently discontinued if any of the following occurs:

- If the LSR(s) do(es) not resolve with the interruption of therapy for 2 weeks, or
- If the LSR(s) recur(s) during bid dosing, or
- If a third drug interruption is needed.

7.5 Subject Discontinuation/Withdrawal from the Study

Subjects may be discontinued/withdrawn from the study for reasons that include, but are not limited to, the following:

- A subject may withdraw from the study at any time at his/her own request, or he/she may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- See Section 1.2 for the data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The discontinuation of specific study centers or of the study are handled as part of Appendix 2.

7.6 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and the study center is unable to contact him/her as described below.

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

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

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.2). Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct. Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing the informed consent form (ICF) may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record the details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Protocol waivers or exemptions may be permitted at the Sponsor's discretion, especially when mitigating factors associated with a global pandemic and other situations that arise that are outside the control of the Sponsor and/or Investigator. Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

8.1 Study Visits

This study will consist of 6 visits as described in the Schedule of Activities (Section 1.2). The maximum amount of blood collected from each subject over the duration of the study will be approximately 20 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1.1 Visit 1 (Screening)

Screening will occur at Visit 1 (Day -90 to Day -7). Subjects can be screened for the study up to approximately 90 days before Baseline. During Screening, the study requirements and procedures will be reviewed and written informed consent/assent will be obtained prior to the initiation of any study-related procedures. Following informed consent, a review of inclusion exclusion will be conducted so that the Investigator can assess if the subject is likely to be eligible for enrollment. Once this is confirmed, the availability of genetic testing confirming the diagnosis of CI and specific subtype will be addressed. Subjects who already have had genetic test documenting ARCI-LI or RXLI types of CI will not be required to provide samples for genetic testing. However, the subject must provide the Investigator with a copy of the genetic report for the source documentation file. Subjects requiring genetic testing, will have a buccal specimen obtained and sent for analysis. Following confirmation of the appropriate genetic subtype, the following procedures will be completed in the Screening period; Demographics, medical history, concomitant medications, physical exam, vital signs, clinical evaluation of extent and location of CI, percent BSA with CI in the Treatment Area, as well as in the VIIS Assessment Area, and

clinical laboratory test as found in Table 7. In addition, VIIS for scaling will be performed for the VIIS Assessment Area and IGA for Scaling and Fissure will be performed for the Treatment Area.

Subjects who meet all inclusion criteria and no exclusion criteria will be randomized to a treatment group stratified by CI subtype. Randomization will be performed as specified in Section 6.3.

8.1.2 Visit 2 (Baseline)

Baseline activities will occur at Visit 2. This visit may be performed either on site or as a remote, tele-medicine visit.

The following will be conducted at the visit:

- The subject will be queried for any changes in health status (ie, change in medications or new health issues) since the previous visit, including concomitant medications and concurrent procedures/therapies
- Abbreviated physical exam/ subject disposition via directed query
- Eligibility will be confirmed. All WOCBP must have a negative UPT.
- Photography per a photographic guide provided by the Sponsor (at select study sites and for all subjects where this visit will be conducted remotely)
- Clinical evaluations will be performed prior to the application of study medication. Confirmation of the percent BSA with CI in the Treatment Area and the VIIS Assessment Area
- VIIS for Scaling will be performed for the VIIS Assessment Area and IGA for Scaling and Fissure will be performed for the Treatment Area.
- Age-appropriate Dermatology Life Quality Index (DLQI) and Itch-Numeric Rating Scale (I-NRS) will be completed by the subject.
- Study personnel will review and dispense the Subject Instruction Sheet and Diary. The subject and parent/guardian (if applicable) will be instructed on how and where to dispense and apply study medication to the Treatment Area and to record applications in the Subject Diary.
- If the visit is being held in clinic, the tubes with study medication will be weighed by study personnel prior to dispensing to subject. If the visit it being held remotely, the subject will weigh the tubes with study medication prior to using. Subjects will apply the first dose of the assigned study medication to all affected skin in the Treatment Area under staff supervision either in person or remotely.
- All AEs post application will be recorded.

8.1.3 Visit 3, Visit 4, and Visit 5

Visit 3 will take place at Week 2 on Day 15 ± 4 days; Visit 4 will take place at Week 4 on Day 29 ± 4 days; and Visit 5 will take place at Week 8 on Day 57 ± 7 days. These visits may be performed either on site or as a remote tele-medicine visit.

The following will be completed at these visits:

- The subject will be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. Any AEs will be documented.
- A UPT will be performed for WOCBP at Visit 4 and Visit 5 only. Note: If the UPT result is positive, the subject must discontinue treatment immediately; and the Investigator must report the pregnancy as detailed in Section 8.4.5 and Appendix 6.
- Photography will be performed at select study site(s) per a photo guide provided by the Sponsor and for all subjects where any of these visits will be conducted remotely.
- Clinical evaluations including local skin reactions and determination of the percent BSA with CI in the Treatment/Assessment Areas and overall percent BSA will be performed.
- VIIS for Scaling will be performed for the VIIS Assessment Area and IGA for Scaling and Fissure will be performed for the Treatment Area.
- Age-appropriate DLQI and I-NRS will be completed by the subject at Visit 5 onlyRecord percent of BSA with CI in the VIIS Assessment Area and the Treatment Area
- Study treatment accountability will be performed, including weighing of all newly dispensed and returned tubes.
- The Subject Diary will be collected, reviewed, and re-dispensed.
- The Subject Instruction Sheet will be re-dispensed as necessary. Subjects will be instructed to continue bid treatment in the morning and evening until the next visit and to record all applications in the Subject Diary.
- The subject will be scheduled for the next visit.

8.1.4 Visit 6 (End of Study)

The EOS visit will occur at Week 12 on Day 85 ± 7 days. Any subject who is discontinued from study prior to Visit 6 (EOS) should complete the procedures listed for EOS during their last study visit or Early Termination visit. This visit may be performed either on site or as a remote visit, although all efforts should be made for an on-site visit.

The following will be completed at this visit:

- The subject will be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. Any AEs will be recorded.
- Age-appropriate DLQI and I-NRS will be completed by the subject.

- Abbreviated physical examination/ subject disposition via directed query, vital signs, clinical laboratory tests
- Photography (select study sites and for all subjects where this visit will be conducted remotely)
- UPT for WOCBP will be performed
- The study staff will perform the clinical evaluations , including local skin reactions and record the percent BSA with CI in the Treatment Area and VIIS Assessment Areas
- VIIS for Scaling will be performed for the VIIS Assessment Area and IGA for Scaling and Fissure will be performed for the Treatment Area.
-
- Study treatment accountability will be performed, including weighing of all returned tubes.
- The Subject Diary will be collected and reviewed.

8.2 Efficacy Assessments

At each visit, the skin affected with CI in the Treatment/Assessment Areas defined at the Baseline Visit will be assessed as described below.

8.2.1 Visual Index for Ichthyosis Severity – Scaling

The Investigator will include subjects when any of the 4 VIIS Assessment Areas have some CI disease. At least 2 of the 4 VIIS Assessment Areas MUST have a scaling score of 3 or more. The upper arm, lower leg/shin, and dorsal foot each include left and right body parts. Therefore, one of each left or right must be designated as the Target (upper arm, lower leg, or dorsal foot) and followed throughout the study for VIIS assessment. The arm, leg, or foot with more severe and higher score will be designated as the Target unless they have the same severity scores, in which case the left or right choice will be at the discretion of Investigator assuming no other issues exists, dictating the choice of left/right. The severity scores will be averaged by the electronic data capture system but the score of the two body parts that have a score of 3 or higher will be used to enroll subjects and used in subsequent assessments.

The location of the CI to be treated and the percent body surface area (BSA) with CI in the Treatment Area **and** in the VIIS Assessment Areas will be recorded prior to application of study medication.

Scaling in the VIIS Assessment Areas will be graded using the 5-point VIIS scale: 0 to 4. This is a visual assessment tool to assist with scoring in 4 specific body sites, so it is essential to include at least 2 or more of the 4 body sites with CI in the Treatment/Assessment Areas. The Assessment Areas are described in Section 4.1.2.1. Visual Index for Ichthyosis Severity "Treatment success" (VIIS-50) is defined as a 50% or greater decrease in VIIS scaling score relative to Baseline at Visit 6 (EOS) calculated using the sum of the scores for 'VIIS body areas' that have a Baseline score ≥ 3.

VIIS severity will be calculated as above using the scores obtained via one of two methods below:

a) On-site visual inspection of the VIIS areas
b) Virtual/ Remote visit comprised of both photographs and tele-medicine utilizing synchronous video conferencing technology. The severity score at each visit will be based off information gathered from both sources to yield one score.

8.2.2 Investigator's Global Assessment

The IGA score is a static evaluation of the overall or "average" degree of severity of a subject's disease, considering all the subject's scaling and fissuring in the Treatment Areas by the Investigator or designee. This evaluation takes into consideration the 2 individual characteristics of CI (scaling and fissuring) with the IGA score at each visit representing the average degree of scaling and fissuring that is eligible for treatment. The Treatment Areas are described in Section 4.1.2.2. The IGA will be assessed using the following 5-point scale shown in Table 3:

Table 3 Investigator's Global Assessment Score (5-Point Scale)

0 =	Clear	No scaling and no roughness, no fissure
1 =	Almost Clear	Occasional fine scales, hardly palpable roughness (mostly smooth) no fissure
2 =	Mild	Small and fine scales predominate, no more than a few large scales, mild roughness on palpation, few fissures may be present
3 =	Moderate	Large rather thick scales predominate, coarse roughness on palpation, few fissures may be present
4 =	Severe	Large coalescent scales dominate, sharp edges on palpation with plate-like hyperkeratosis, many fissures may be present

IGA severity will be calculated as above using the scores obtained via one of the two methods below:

c) On-site visual inspection
d) Virtual/remote visit comprised of both photographs and tele-medicine utilizing synchronous videoconferencing technology. The severity score at each visit will be based off information gathered from both sources to yield one score.

8.2.3 Itch-Numeric Rating Scale

Pruritus will be assessed with a self-administered Patient Reported Outcome questionnaire using the I-NRS at Visit 2 (Baseline), Visit 5, and at Visit 6 (EOS). Subjects will indicate itch severity by circling the integer that best describes the worst level of itching due to CI in the past 24 hours on an 11-point scale anchored at 0 representing "no itching" and 10 representing "worst itch imaginable." (see Appendix 11). The study staff should review the I-NRS with each subject and

ask him/her to indicate the response that best describes his/her experience. Pruritus assessed by this evaluation should be reported as an AE only if therapy is required.

8.2.4 Percent Body Surface Area with Active Congenital Ichthyosis in the Treatment/Assessment Areas

The percent BSA with active CI within the Treatment Area will be calculated at Visit 1 (Screening). The Treatment Area includes all affected skin **excluding** the hands, face, neck, scalp and genitalia. This calculation is confirmed at Visit 2 (Baseline) and assessed at all follow-up visits. The minimum affected area to be treated will be no less than 10% and no more than 90% of the whole BSA at Visit 1 (Screening). In addition, the percent BSA with active CI within the designated VIIS /Assessment Areas will be calculated at Visit 1 (Screening) and at all follow-up visits. Note that the Treatment Area is at least equal to or larger than the VIIS Assessment Area. Based on the Treatment and VIIS Assessment Areas selected in a given subject and the extent of his/her disease, these two areas may or may not be the same. Two examples are provided below for clarity:

	Treatment Area % BSA	VIIS Assessment area % BSA
Subject 1	90% (entire body minus hands, face, neck, scalp, genitalia)	24% (upper back, upper arms, lower legs and dorsal feet)
Subject 2	70%	13% (upper back and upper arms)

8.2.5 Dermatology Life Quality Index

The DLQI (Dermatology Quality of Life Index), is a dermatology-specific Quality of Life instrument. Age-appropriate DLQI will be completed at Visit 2 (Baseline), Visit 5, and Visit 6 (EOS). The standard DLQI is a questionnaire designed for subjects ≥ 16 years of age that measures the impact of skin disease on the previous week's quality of life. There are 10 questions related to the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, treatment (see Appendix 9). Questions are scored from 0 to 3 with a possible score range from 0 (no impact of skin disease on quality of life) to 30 (maximum impact on quality of life). The score ranges are shown in Table 4.

Table 4 Dermatology Life Quality Index Scale

0 to 1 =	No effect on patient's life
2 to 5 =	Small effect

6 to 10 =	Moderate effect
11 to 20 =	Very large effect
21 to 30 =	Extremely large effect.

The minimal clinically important difference (MCID) is the minimum difference in score that is meaningful for a subject. This is considered 4 for inflammatory skin diseases.

Children's DLQI will be used for subjects < 16 years of age to measure the impact of skin disease on the previous week's quality of life. There are 10 questions related to the following topics: symptoms and feelings, leisure, school or holidays, personal relationships, sleep, treatment (see Appendix 10). Questions are scored from 0 to 3 with a possible score range from 0 (no effect on child's life) to 30 (extremely large effect). The score ranges are shown in Table 5.

Table 5 Children's Dermatology Life Quality Index Scale

0 to 1 =	No effect on child's life
2 to 6 =	Small effect
7 to 12 =	Moderate effect
13 to 18 =	Very large effect
19 to 30 =	Extremely large effect.

8.3 Safety Assessments

The planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.2).

8.3.1 Physical Examinations

A brief physical examination will be performed at Visit 1 (Screening).Abbreviated examination/ subject disposition will be conducted at Visit 2 (Baseline) to identify any changes since the Screening visit and at Visit 6 EOS to assess for any changes during the study. The examination will evaluate head and neck, dermatological, cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait body assessments. Abnormalities at Visit 1 (Screening) and Visit 2 (Baseline) prior to treatment will be recorded as medical history. Any new or worsening abnormalities at Visit 6 (EOS) will be recorded as AEs.

8.3.2 Vital Signs

Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured at Visit 1 (Screening) and Visit 6 (EOS). Assessments will be made after the subject has rested in a seated position for at least 5 minutes in a quiet setting without distractions (eg, television, cell phones). Height and weight will only be measured at Visit 1 (Screening).

8.3.3 Local Skin Reactions

At every study visit (except Screening), the Investigator or designee will evaluate LSRs known to be associated with retinoids (burning/stinging, erythema, erosions, and edema) or other causes regardless of blinded causality assessment within the areas treated with study medication using a 4-point ordinal scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Note: At Visit 2 (Baseline), the LSR assessment must be performed prior to the application of study medication. Only LSRs that require medical intervention (eg, prescription medication) or that require withholding application of the study medication will be documented as AEs. Any LSRs that are not listed above will be recorded as AEs. For drug interruption due to LSRs, refer structured drug interruption scheme (drug holiday) described in Section 7.4.

8.3.4 Electrocardiograms

Electrocardiogram monitoring will not be performed in this study.

8.3.5 Clinical Safety Laboratory Assessments

Urine and blood samples will be collected from each subject for safety laboratory analyses at Visit 1 (Screening) and Visit 6 (EOS).

Subjects must be fasting (at least 8 hours) for Visit 1 (Screening) and, if possible, for Visit 6 (EOS); however, if a subject arrives at the clinic for Visit 6 (EOS) without fasting for at least 8 hours, laboratory specimens may be collected as non-fasting, at the discretion of the Investigator, and with the appropriate fasting status documented on the laboratory requisition form.

For subjects that will have the Visit 6 (EOS) conducted remotely, urine and blood samples may be collected by a home health care provider supplied by the Sponsor.

See Appendix 3 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.2) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease unless judged by the Investigator to be out of range to a greater degree than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study medication should be repeated until the values, stabilize, return to normal or Baseline, or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/Baseline within a period judged reasonable by the Investigator, the etiology should be identified, and the Sponsor should be notified.

- All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.2).
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE, AE, dose interruption), then the results must be recorded in the eCRF.

Any new or worsening of clinically significant abnormalities at Visit 6 (EOS) will be recorded as AEs.

8.4 Adverse Events

All AEs will be recorded. At each post-Baseline Visit, subjects will also be questioned specifically about the status of any ongoing AEs.

The definitions of an AE or SAE can be found in Appendix 4.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the subject to discontinue the study (see Section 7.0). The trial blind may be broken for an individual only if knowledge of the IMP is essential for clinical management of the subject.

8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from signing the ICF until the Visit 6 (EOS) at the time points specified in the Schedule of Activities (Section 1.2).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study medication or study participation, the Investigator must promptly notify the Sponsor.

The methods of recording, evaluating, and assessing the causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.6). Further information on follow-up procedures is given in Appendix 4.

8.4.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and the Sponsor's policy and forwarded to the Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

A UPT will be performed at Visit 2 (Baseline), Visit 4, Visit 5, and Visit 6 (EOS) for WOCBP. Women who are pregnant or breastfeeding may not be administered TMB-001 ointment.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6 Adverse Events of Special Interest

No events will be considered as AEs of special interest for this study.

8.4.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Disease attributes that are associated with underlying disease condition should not be reported as AEs. Local skin reactions associated with retinoids should not be reported as AEs unless the LSRs required medical intervention or withholding application of study medication (refer Section 8.3.3 for complete details).

8.5 Treatment of Overdose

Overdose in this study can be defined as either oral ingestion of a tube of TMB-001 or applying the TMB-001 ointment more than the protocol specified regimen of twice daily.

Oral ingestion of a tube of TMB-001 ointment 0.1% would result in less exposure than achieved with the recommended dosage of oral isotretinoin. Consequently, the theoretical occurrence of symptoms of overdosage (eg, hypervitaminosis A) is highly unlikely.

If a subject does receive an overdose of TMB-001 ointment, the subject should be counseled about the teratogenicity of isotretinoin and counseled on the prevention of pregnancy. Any WOCBP must be evaluated for pregnancy and must be warned to avoid pregnancy per the contraceptive measures outlined in the protocol for at least 1 month after overdose. Men should use a condom or avoid reproductive sexual activity with a female who is or might become pregnant for at least 1 month after an overdose. Subjects who present with an overdose should not donate blood for at least 1 month.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AEs, SAEs, and laboratory abnormalities for 1 month after the overdose.
3. Obtain a plasma sample for pharmacokinetic analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Genetics

To be eligible for the study, subjects must have moderate to severe CI that has been genetically confirmed to be of either the ARCI-LI or RXLI subtype. For ARCI-LI subjects, enrollment is not limited to Transglutaminase 1 mutations. Other genetically confirmed ARCI-LI mutations can potentially be enrolled as long as the phenotype is consistent with ARCI-LI and the other inclusion criteria are met, as determined by the Investigator. Subjects requiring genetic test confirmation will have the testing performed by an independent laboratory after the Investigator or designee has determined they are likely to be otherwise eligible for enrollment. A buccal sample from the subject will be taken and sent to the laboratory for genotyping. Congenital Ichthyosis XomeDxSlice will be used to diagnose both RXLI and the ARCI-LI. subtype of CI. GeneDx tests detect transglutaminase mutations in the TGM1 gene, X-linked recessive steroid sulfatase mutations in the STS gene, and additionally analyzes 47 other genes linked to CI. This is a multi-gene panel testing so that all known causes of CI can be confirmed/ruled-out since there is phenotypic overlap between the subtypes (including STS). The tests are considered Laboratory Developed Tests (LDTs) and are thus regulated per US regulations 42 CFR 493 and the laboratory is accredited by the College of American Pathologists.

See Appendix 7 for Information regarding genetic research.

8.9 Biomarkers

Biomarkers will not be evaluated in this study.

8.10 Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

9.2 Sample Size Determination

This is the first study of TMB-001 using the VIIS index. No formal power calculations were performed to establish sample size since there were no VIIS response data available. A sample

size of 45 subjects (15 per treatment group) has been selected to provide initial data on VIIS response and to enable formal sample size calculations for future studies, as well as to assist in dose selection for Phase 3 study.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets are defined in Table 6.

Table 6 Analysis Sets

Analysis Set	Description
Intent-to-Treat (ITT) Population	All randomized subjects who received at least one dose of study medication . Subjects will be analyzed according to the treatment they are planned to receive according to the randomization schedule.
Per-Protocol (PP) Population	Subset of the ITT population consisting of subjects who 1) meet all inclusion/exclusion criteria that would affect the treatment evaluation, 2) apply ≥ 80% but ≤ 120% of the planned doses of study treatment, 3) who had a VIIS measurement at Visit 6 (EOS), and 4) have no major protocol violations that would affect the treatment evaluation. The final definition of the PP population will be presented in the SAP. Subjects will be analyzed according to the treatment they are planned to receive according to the randomization schedule.
Safety Population	All subjects randomly assigned to study treatment and who take at least 1 dose of study medication. Subjects will be analyzed according to the treatment they actually receive.

Abbreviations: ITT = intent-to-treat; PP = per-protocol; SAP = Statistical Analysis Plan.

9.4 Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses and procedures for accounting for missing, unused, and spurious data. Efficacy analyses will be performed on both the intent-to-treat (ITT) and per-protocol (PP) populations with the ITT population considered primary.

This section is a summary of the planned statistical analyses of the primary and secondary endpoints. All statistical analyses and summaries will be prepared using SAS unless otherwise stated.

Demographic and Baseline characteristics will be summarized by treatment group for the Safety, ITT, and PP populations. Frequency counts and percentages will be reported for categorical data and sample size, mean, median, standard deviation (SD), minimum (min), and maximum (max) will be reported for the continuous variables.

All statistical analyses and summaries will be prepared using SAS unless otherwise stated. All subjects enrolled in the study who are dispensed and apply study medication at least once will be included in the analysis of safety and will be considered the Safety population. All randomized

subjects who received at least one dose of study medication will be considered the ITT population. The PP population will be a subset of the ITT population consisting of subjects who: 1) meet all inclusion/exclusion criteria that would affect the treatment evaluation, 2) apply ≥ 80% but ≤ 120% of the planned doses of study treatment, 3) who had a VIIS measurement at Visit 6 (EOS), and 4) have no major protocol violations that would affect the treatment evaluation. The final definition of the PP population will be presented in the SAP.

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: sample size, mean, SD, median, min, and max.
- Categorical variables: frequencies and percentages.

Individual subject data will be presented in listings.

9.4.1 Efficacy Analyses

All efficacy analyses will be performed on both the ITT and PP populations with the ITT population considered primary. Other post hoc analysis may be conducted using a modified ITT population. Any such analyses will be fully described in the SAP prior to database lock.

9.4.1.1 Primary Efficacy Endpoint

The proportion of subjects achieving VIIS-50 (≥ 50% reduction from Baseline for VIIS scaling score for the sum of the scores for 'VIIS body areas' who had a Baseline score ≥ 3) at Visit 6 (EOS) relative to Baseline will be the primary efficacy endpoint and time point used to compare active treatment to vehicle. Treatment groups will be compared at Visit 6 (EOS) using the Cochran-Mantel-Haenszel (CMH) Test stratified by CI subtype and corresponding 95% confidence intervals will be calculated for the difference in proportions for the treatment groups.

9.4.1.2 Secondary Efficacy Endpoints

The proportion of subjects achieving IGA treatment success will be the key secondary endpoint. For this endpoint, the IGA score will be dichotomized to "treatment success" or "treatment failure" where "treatment success" is defined as at least a 2-grade decrease in severity score relative to Baseline. Active treatment will be compared with vehicle at Visit 6 (EOS) using the CMH test stratified by CI subtype and 95% confidence intervals will be calculated for the difference in proportions for the treatment groups.

Additionally, one secondary endpoint is the time to achieve VIIS-50 that is maintained at the next observation. If VIIS-50 is first achieved at Visit 6 (EOS), then the endpoint is considered to have been met. A time to event analysis will be completed using the Kaplan-Meier method and log rank test to compare active treatment with vehicle.

For each of the other secondary efficacy endpoints (VIIS scaling, IGA, and I-NRS), the following summaries will be prepared at Visits 3, 4, 5, and 6 (EOS) (as applicable) by treatment group for each CI subtype and overall:

- Frequency distribution of observed scores;
- Frequency distribution of change from Baseline;
- Shift tables for changes from Baseline to Visits 3, 4, 5, and 6; and,
- Frequency distribution of treatment success rates.

Success rates between treatment groups will be compared at Visit 6 (EOS) using the CMH Test stratified by CI subtype, and 95% confidence intervals will be calculated for the difference in proportions for the treatment groups. The VIIS scaling success is defined as a $\geq 50\%$ reduction from Baseline for body sites that had a Baseline score ≥ 3. For IGA, success is defined as a ≥ 2-point reduction from Baseline. For I-NRS, success is defined as ≥ 4-point reduction from Baseline.

Descriptive statistics (including mean, median, SD, min, and max) for observed and change from Baseline values in the DLQI and percent BSA affected in the Treatment/Assessment Areas at each visit will be presented by treatment group for each CI subtype and overall.

For VIIS and I-NRS, the treatment groups will be compared with respect to the change from Baseline using a mixed model of repeated measures (MMRM) including terms for treatment, visit, treatment by visit interaction, and the Baseline value serving as the covariate. From the model, the active to vehicle treatment differences will be estimated. Additionally, two-sided confidence intervals will be provided.

9.4.2 Safety Analyses

All subjects enrolled in the study who were dispensed study medication and who applied study medication at least once will be included in the analysis of safety and will be considered the Safety population.

All AEs reported during the study will be listed, documenting onset, whether therapy was required, any change in study treatment dosing, severity, possible relationship to study treatment, and outcome. Verbatim terms on the eCRFs will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occur or worsen in severity after the first administration of study treatment and prior to 30 days after the last administration of study treatment. All reported TEAEs and incidence rates will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to study treatment by treatment group.

Treatment-emergent AEs by maximum severity, TEAEs by relationship to study treatment, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated for each treatment group. Commonly occurring TEAEs, ie, those that occur in 5% or more of the subjects in either treatment group, will be summarized using descriptive statistics.

All laboratory test results, vital signs measurements, and weight will be summarized for each treatment group using descriptive statistics for raw numbers and change from Baseline. The incidence of treatment-emergent abnormal laboratory and vital signs values will also be summarized using descriptive statistics.

9.4.3 Other Analyses

9.4.3.1 Physical Examinations

Findings from physical examinations (head and neck, cardiovascular, dermatological, respiratory, gastrointestinal [abdomen], and gross motor and gait assessments) will be recorded in the medical history (from assessment at Visit 1 [Screening] and Visit 2 [Baseline]) or as AEs (from assessment at Visit 6 [EOS]).

9.4.3.2 Vital Signs

Descriptive statistics of vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) at Visit 1 (Screening) and Visit 6 (EOS), and change from baseline, will be provided by treatment group.

9.4.3.3 Clinical Laboratory Tests

Clinical laboratory tests will be evaluated for any material changes during the study period. All laboratory data (hematology, chemistry, and urinalysis) will be listed and reported in the units received by the laboratory. Summary tables by analyte and by out of range flag, at Visit 1 (Screening) and Visit 6 (EOS), and change from baseline, will be presented to facilitate the evaluation of change from Visit 1 (Screening) to Visit 6 (EOS).

9.4.3.4 Urine Pregnancy Test

The UPT results (if applicable) from Visit 2 (Baseline), Visit 4, Visit 5, and Visit 6 (EOS) will be provided in a listing.

9.4.3.5 Local Skin Reactions

The LSRs (burning/stinging, erythema, erosions, and edema) and others will be summarized by frequency of each individual LSR for each treatment group. Change from Baseline in LSRs will be categorized into “worsened” and “same or improved” and will be tabulated.

9.4.4 Missing Data

Data summaries and analyses will use observed data only without imputation of missing values. Supplementary analysis will be performed to investigate the impact of data imputation on the primary endpoint as follows:

1. By assuming that subjects with missing data are treatment successes ("best case"); and
2. By assuming that subjects in the Vehicle group with missing data are "treatment success" and that subjects in the TMB-001 groups with missing data are treatment failures ("worst case").
3. By assuming that subjects with missing data maintain their last observed rating from which treatment success or failure will be derived at Visit 6 ("LOCF").

9.4.5 Extent of Exposure

The total amount of study medication used (grams of study medication applied) will be calculated from the weights of the returned study medications. Descriptive statistics (mean, median, SD, min, and max) will be determined for the total amount of study medication used by each subject by treatment group.

9.4.6 Dosing Compliance

Descriptive statistics will be used to summarize study treatment compliance for the ITT population. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% but no more than 120% of the expected number of applications or dose.

Measures of overall study treatment compliance will include the duration of treatment (number of days dosed), the total number of applications (determined from the actual number of applications reported by the subject), quantity of dose, and the percent of expected doses applied. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% but no more than 120% of the expected number of applications or dose.

9.5 Interim Analyses

No interim analysis for efficacy is planned.

9.6 Monitoring Committee

No Safety Monitoring Committee is planned for this study.

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
AE	Adverse event
ARCI-LI	Autosomal recessive congenital ichthyosis-lamellar ichthyosis
β-hCG	beta human chorionic gonadotropin
bid	Twice daily
BSA	Body surface area
CFR	Code of Federal Regulation
CI	Congenital ichthyosis
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
DLQI	Dermatology Life Quality Index
eCRF	Electronic case report form
EOS	End of Study
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormonal replacement therapy
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
I-NRS	Itch-Numeric Rating Scale
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LI	Lamellar ichthyosis
LSR	Local skin reaction
Max	Maximum
MCID	Minimal clinically important difference

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed model of repeated measures
PP	Per-protocol population
PT	Preferred term
RA	Retinoic acid
RXLI	Recessive X-Linked ichthyosis
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper Limit of Normal
UPT	Urine pregnancy test
US	United States
UV	Ultraviolet light
VIIS	Visual Index for Ichthyosis Severity
VIIS-50	Visual Index for Ichthyosis Severity – Scale “treatment success”
WOCBP	Women of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 8). The study will not start at any study center at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with enough, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.
- The Sponsor or its representative will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, the Sponsor or representative physician or

an Investigator might know a subject's identity and have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

Administrative Structure

The Sponsor of this study is Timber Pharmaceuticals, LLC (Address: 50 Tice Boulevard, Suite A26, Woodcliff Lake, NJ 07677). Study administrative structure including emergency contacts, Clinical Research Organization (CRO), Laboratory, and ancillary services can be found in the Investigator Study Binder.

Medical Monitor

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IQVIA Biotech

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Study Site Initiation

The Investigator must not screen any subject prior to completion of the study initiation visit, conducted by CRO. This initiation visit will include a detailed review of the protocol and study procedures.

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the ClinicalTrials.gov database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable

from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Investigator Study Binder.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

- The results of this study in aggregate may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments. No individual site related study results will be allowed to be presented.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

Subjects must be fasting (at least 8 hours) for Visit 1 (Screening) and, if possible, for Visit 6 (EOS); however, if a subject arrives at the clinic for Visit 6 (EOS) without fasting for at least 8 hours, laboratory specimens may be collected as non-fasting, at the discretion of the Investigator, and documented as such on the laboratory requisition form.

- The tests detailed in Table 7 will be performed by the central laboratory.
- Local laboratory results are only required if the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices:	White Blood Cell Count with Differential:	
	Red Blood Cell (RBC) Count	Mean Corpuscular Volume (MCV)	Neutrophils	
	Hemoglobin	Mean Corpuscular Hemoglobin (MCH)	Lymphocytes	
	Hematocrit	% Reticulocytes	Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and Direct Bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (Fasting)	Calcium	Alkaline Phosphatase	
Routine Urinalysis	• Specific Gravity • pH, Glucose, Protein, Blood, Ketones, (Bilirubin, Urobilinogen, Nitrite, Leukocyte Esterase) by Dipstick • Microscopic Examination (if Blood or Protein Is Abnormal)			
Other Screening Tests	• Urine Human Chorionic Gonadotropin (hCG) Pregnancy Test (as Needed for Women of Childbearing Potential)[a] • Serology (human immunodeficiency virus [HIV] Antibody)			

Laboratory Assessments	Parameters
	• All study-required laboratory assessments will be performed by a central laboratory, with the exception of urine pregnancy testing. The results of each test must be entered into the (e)CRF.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to IQVIA Biotech Safety in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by IQVIA Biotech Safety. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to IQVIA Biotech Safety.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, or unknown (unable to judge).
  - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
  - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
  - "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
  - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
  - All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, eg, because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to IQVIA Biotech Safety. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to IQVIA Biotech Safety.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by IQVIA Biotech Safety to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide IQVIA Biotech Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor/IQVIA Biotech Safety within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to IQVIA Biotech Safety via Paper CRF

- E-mail transmission of the SAE paper CRF is the preferred method to transmit this information to IQVIA Biotech Safety with Facsimile transmission as back-up method.
- In rare circumstances and in the absence of e-mail/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE eCRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Investigator Study Binder. All SAEs must also be reported to IQVIA Biotech Safety within 24 hours of first awareness of the event. A paper SAE Report Form should be completed and submitted via e-mail to Safety-Inbox.Biotech@IQVIA.com or faxed to +1-919-313-1412.

Appendix 5 Excluded Medications/Therapy

Excluded medications/therapy are listed in Section 5.2 and Section 6.5. The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF.

Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8 below.

Table 8 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment.

Pregnancy Testing:

- WOCBP will only be included in the study after a confirmed negative urine pregnancy test at Visit 2 (Baseline). The UPT must have a minimum sensitivity of 25 mIU beta human chorionic gonadotropin.
- Additional pregnancy testing will occur at times specified in the schedule of assessments during the treatment period, at the Visit 6 (EOS), and as required locally.

Collection of Pregnancy Information

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.4.5. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will be withdrawn from the study.

Appendix 7 Genetics

Use/Analysis of Deoxyribonucleic Acid (DNA)

- Genetic variation may impact a subject's response to study treatment, susceptibility to, and severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood/saliva /buccal sample will be collected for DNA analysis from consenting subjects.
- DNA samples will be used for research related to topical iso tretinoin for treatment of congenital ichthyosis and related diseases. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analyzed to detect transglutaminase mutations in the TGM1 gene, X-linked recessive steroid sulfatase mutations in the STS gene. Additionally, analysis may be performed to look at other genes linked to CI. Further analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- DNA samples will be analyzed using Congenital Ichthyosis XomeDxSlice to diagnose both RXLI and ARCI-LI. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study treatment or study treatments of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.
- The DNA samples will be handled by an independent laboratory and will be destroyed upon the completion of study. They will be in a secure storage space with adequate measures to protect confidentiality. The tests are considered Laboratory Developed Tests (LDTs) and are thus regulated per US regulations 42 CFR 493 and the laboratory is accredited by the College of American Pathologists.

Appendix 8 Signature of Investigator

PROTOCOL TITLE: A Randomized, Parallel, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Two Concentrations of Topical TMB-001 for the Treatment of Congenital Ichthyosis

PROTOCOL NO: 235-9051-202

VERSION: Original Protocol

This protocol is a confidential communication of Timber Pharmaceuticals, LLC. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

Appendix 9 Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: ..... **Date:** .....

Name: ..... **Score:** .....

Address: ..... **Diagnosis:** .....

.....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
2.	Over the last week, how embarrassed or self conscious have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
3.	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
4.	Over the last week, how much has your skin influenced the clothes you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
5.	Over the last week, how much has your skin affected any social or leisure activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
6.	Over the last week, how much has your skin made it difficult for you to do any sport?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
7.	Over the last week, has your skin prevented you from working or studying?	Yes No	❒ ❒	Not relevant	❒
	If "No", over the last week how much has your skin been a problem at work or studying?	A lot A little Not at all	❒ ❒ ❒		
8.	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
9.	Over the last week, how much has your skin caused any sexual difficulties?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
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?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒

Please check you have answered EVERY question. Thank you.

DERMATOLOGY LIFE QUALITY INDEX (DLQI) - INSTRUCTIONS FOR USE

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

SCORING

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question 7, 'prevented work or studying'	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

HOW TO INTERPRET MEANING OF DLQI SCORES

0 – 1	no effect at all on patient's life
2 – 5	small effect on patient's life
6 – 10	moderate effect on patient's life
11 – 20	very large effect on patient's life
21 – 30	extremely large effect on patient's life

REFERENCES

Finlay AY and Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19:**210-216.

Basra MK, Fenech R, Gatt RM, Salek MS and Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159:**997-1035.

Hongbo Y, Thomas CL, Harrison MA, Salek MS and Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol* 2005; **125:**659-64.

There is more information about the DLQI, including over 85 translations, at www.dermatology.org.uk. The DLQI is copyright but may be used without seeking permission by clinicians for routine clinical purposes. For other purposes, please contact the copyright owners.

Appendix 10 Children's Dermatology Life Quality Index

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

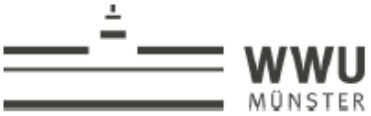
Hospital No
Name: Diagnosis: CDLQI SCORE:
Age:
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time?** **OR** was it **holiday time?**	**If school time**: Over the last week, how much did your skin problem affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school Very much Quite a lot Only a little Not at all Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question. Thank you.

Appendix 11 Itch-Numeric Rating Scale



Validated scales according to IFSI SIG / EADV Task Force Pruritus.

Contact: Center for Chronic Pruritus, University Hospital Münster.
Email: KCPadministration@ukmuenster.de

No license. Please reference as:
Phan NQ et al. Acta Derm Venereol. 2012;92:502-7
Verweyen E at al. Acta Derm Venereol. 2019;99:657-66

1. Numerical Rating Scale. On a scale from 0 (no itch) to 10 (worst imaginable itch)…										
…how was your itch, on average, within the past 24 hours? Please select one number.										
0	1	2	3	4	5	6	7	8	9	10
…how was your worst itch in the past 24 hours? Please select one number.										
0	1	2	3	4	5	6	7	8	9	10