Cover Page

Study title: The ASCEND Study: A Phase III, Multicenter, Double Blinded Vehicle Controlled Study of TMB-001 - with a Parallel Optional Maximal Use Arm - in the Treatment of RXLI (Xlinked) or ARCI Ichthyosis in Subjects Aged ≥6 Years
LEO Pharma number: TMB01-301
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TITLE PAGE

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Protocol Number: TMB01-301

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

Short Title: The ASCEND Study: Evaluating TMB-001 in the treatment of RXLI or ARCI-Ichthyosis

Study Phase: 3

Sponsor Name: Timber Pharmaceuticals, LLC

Legal Registered Address: 110 Allen Road, Suite 401, Basking Ridge, NJ 07920

Investigational New Drug (IND) number: 122,058

EudraCT number 2022-000459-35

Date of Protocol: 25 July 2022

Version: 2.0

Protocol Amendment 1

APPROVAL SIGNATURE PAGE

Sponsor Signatory:

I have read this protocol in its entirety and approve its contents:

[redacted] **Chief Medical Officer**	**Date**

The Medical Monitor's name and contact information can be found in Appendix 1.

The Investigator's Agreement Page is provided in Appendix 6

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PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title	The ASCEND Study: A Phase III, Multicenter, Double Blinded Vehicle Controlled Study of TMB-001 - with a Parallel Optional Maximal Use Arm - in the Treatment of RXLI (X-linked) or ARCI Ichthyosis in Subjects Aged ≥6 Years
Study Product	TMB-001 (previously PAT-001) (Isotretinoin) Ointment (0.05%)
IND Number	122058
Protocol Number	TMB01-301
Phase of Development	III
Study Design	This randomized, double-blind, vehicle-controlled Phase III study is designed to evaluate the efficacy and safety of topical TMB-001 0.05% ointment for the treatment of recessive X-linked ichthyosis (RXLI) and autosomal recessive congenital ichthyosis (ARCI). In addition, a subset of preselected centers will recruit subjects in parallel for enrollment into an Optional Maximal Use arm for evaluation of the systemic exposure and safety of topical TMB-001 0.05% ointment for the treatment RXLI or ARCI. The study has three periods: • **Period 1 – Induction (3 weeks):** At the beginning of the 3-week induction period, eligible subjects will be randomized (2:1 ratio) to either TMB-001 0.05% once-a-day (QD) or Vehicle QD treatment, with use of mandatory standardized bland emollient (Cetaphil™) provided by the Sponsor. • **Period 2 – Treatment (9 weeks):** The dosing frequency in the 9-week treatment period will be increased in each treatment group to TMB-001 0.05% or Vehicle twice a day (BID). Mandatory bland emollient will be discontinued. • **Period 3 – Maintenance (12 weeks):** At Week 12, eligible subjects in the TMB-001 treatment group will be randomized (1:1 ratio) to open-label treatment with TMB-001 0.05% BID or QD. To be eligible, subjects must have achieved a ≥1-point reduction in Investigator Global Assessment (IGA) score from Baseline. Subjects with <1-point reduction in IGA score from Baseline will be discontinued from the study. Vehicle-treated subjects who achieved <1-point reduction in IGA score from Baseline are eligible to cross over to the TMB-001 0.05% BID treatment group. Subjects with a ≥1-point reduction in IGA score from Baseline will be discontinued from the study. **<u>Optional Maximal Use Arm</u>** Adult and pediatric subjects, at a subset of preselected centers, will be enrolled in an open-label Optional Maximal Use arm to evaluate the systemic exposure and safety of topical TMB-001 0.05% ointment for the treatment of CI under maximal use conditions. Initially, adult CI subjects (≥17 years; n=16) and pediatric subjects (12-16 years; n=7-9) will be dosed for 14 days with TMB-001 0.05% BID. Following an interim pharmacokinetic (PK) analysis and based on the exposure data for subjects aged ≥12 years, pediatric subjects aged 6 to 11 years (n=7-9) will begin dosing with TMB-001 0.05% BID for 14 days. Following the 14-day PK assessment period, subjects will

	receive TMB-001 0.05% BID treatment for 10 weeks to provide additional safety and limited efficacy data.
Sample Size	Approximately 110 subjects **Optional Maximal Use Arm:** approximately 32 subjects
Study Duration	Up to 90-day screening + 24 weeks treatment **Optional Maximal Use Arm:** Up to 90-day screening, 14-day treatment period for intensive PK sampling followed by 10 weeks of open-label treatment
Study Eligibility Criteria	Subjects must fulfill all of the following **inclusion criteria** to be eligible for participation: 1. Subject is male or female, 6 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 2 acceptable forms of birth control. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and 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 4. 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 of birth control for the duration of the study. 4. Subject has clinical diagnosis of CI based upon phenotype and has a genetic confirmation of either ARCI (including but not exclusively transglutaminase 1-deficient, ALOX-12B) or RXLI (e.g., deletion of steroid sulfatase gene) subtypes of CI. Other genetically confirmed ARCI mutations can potentially be enrolled as long as the phenotype is consistent with ARCI and the other inclusion criteria are met, as determined by the Investigator (Appendix 5). 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 body surface area (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). • **For the Optional Maximal Use arm**: The amount of CI affected skin in the Treatment Area at Baseline will be between a minimum of 75% and maximum of 90% of the total BSA. 6. Documented history of moderate to severe disease at Screening**.** Subject's designated Visual Index for Ichthyosis Severity (VIIS) Assessment Areas at Baseline (**not applicable for Optional Maximal Use arm**) 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 kneecap), 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's IGA score in the Treatment Area at Baseline must be 3 or more. 8. 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. 9. 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 Areas or exposes the subject to an unacceptable risk by study participation. A subject is ineligible to enter the study if he/she meets 1 or more of the following **exclusion 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 (e.g., atopic dermatitis) unrelated to ichthyosis. 3. Subject has phenotypic clinical presentation and/or genetic abnormality consistent with non-lamellar type or syndromic ichthyoses (including but not exclusively KRT1, KRT10, KRT2, GJB3, GJB4, CDSN). 4. Subject, in the Treatment Areas, has used: (*a*) any 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, in the Treatment Areas, has used TMB-001 in the past or oral isotretinoin in the past 12 months (**not applicable for Optional Maximal Use arm**) 6. Subject has used any topical products in the Treatment Areas, including bland emollients, on Visit 2 (Baseline). 7. Subject has used ultraviolet treatment within 4 weeks prior to Visit 2 (Baseline). 8. 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.* 9. Subject is immunosuppressed (e.g., 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 or five half-lives prior to Visit 2 (Baseline). 13. Subject has lesions suspicious for skin cancer (if skin cancer is not ruled out by biopsy), a known personal or immediate family history of squamous cell carcinoma of the skin or melanoma or untreated skin cancers within the Treatment 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 x Upper Limit of Normal (ULN) and/or creatinine >1.5 x 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 (e.g., 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.
Study Objectives	• **Primary Objective** To ascertain the efficacy of TMB-001 0.05% topical ointment as a treatment for CI compared with Vehicle during a 12-week treatment. • **Key Secondary Efficacy Objectives** **1.** To ascertain the efficacy of TMB-001 0.05% topical ointment at Week 12 using the VIIS-50 scaling score. **2.** To ascertain the efficacy of TMB-001 0.05% topical ointment at Week 12 using the IGA-scaling and fissuring scores. **3.** To evaluate the effect of TMB-001 0.05% topical ointment on subject Worst Itch-QoL scores at Week 12 in subjects with baseline Itch-Numeric Rating Scale (I-NRS) of ≥7 **Other Secondary Efficacy Objectives** **4.** To ascertain the efficacy of TMB-001 0.05% topical ointment at Week 12 using different levels of VIIS-scaling and IGA-scaling and fissuring scores. **5.** To determine optimal maintenance therapy with TMB-001 0.05% topical ointment using the IGA-scaling and fissuring scores. **6.** To determine optimal maintenance therapy with TMB-001 0.05% topical ointment using VIIS-scaling scores. • **Patient-reported Outcome Measures** **7.** To evaluate the effect of TMB-001 0.05% topical ointment on subject Quality of Life (QoL) during the 12-week treatment period and subsequent 12-week maintenance period. • **Safety Objective** **8.** To investigate the safety of topically applied TMB-001 0.05% ointment. **9.** To evaluate incidence of suspected allergic contact dermatitis supplemented by subsequent confirmatory clinical testing. **<u>Optional Maximal Use Arm</u>**

	• **Primary Objective** To determine systemic exposure of isotretinoin and metabolites after single or multiple applications of TMB-001 0.05% ointment in subjects with RXLI or ARCI. • **Secondary Objective** To compare systemic exposure of isotretinoin and metabolites after single or multiple applications of TMB-001 0.05% ointment cross-trial for PK parameters obtained for oral isotretinoin (single dose 80 mg) in healthy volunteers. • **Safety Objective** To assess local safety and tolerability of TMB-001 0.05% ointment in adult and pediatric subjects for up to 12 weeks.
Study Endpoints	• **Primary Endpoint** Comparison of proportions of subjects with ≥2-point changes from Baseline in IGA-scaling and fissuring scores in the Treatment Area at Week 12 between TMB-001 0.05% and vehicle-treated subjects. • **Key Secondary Efficacy Endpoints** **1.** Comparison of proportion of subjects who achieve 50% reduction from Baseline in VIIS-scaling scores at Week 12 in all areas with Baseline VIIS score ≥3 between TMB-001 0.05% and vehicle-treated subjects. **2a.** Comparison of proportion of subjects with IGA-scaling and fissuring scores of clear or almost clear at Week 12 between TMB-001 0.05% and vehicle-treated subjects. **2b.**Comparison of proportions of subjects who achieve IGA-scaling severity sub-score improvement ≥ 2-points from Baseline to Week 12 between TMB-001 0.05% and vehicle-treated subjects. **3.** Comparison of proportion of subjects with ≥4-point improvement from baseline in Worst Itch-QoL scores at Week 12 in subjects with baseline Itch-Numeric Rating Scale (I-NRS) of ≥7 between TMB-001 0.05% and vehicle-treated subjects. • **Other Secondary Efficacy Endpoints** **4a.**Comparison of proportion of subjects who achieve 25% reduction from Baseline in VIIS-scaling scores at Week 12 in all areas with Baseline VIIS score ≥3 between TMB-001 0.05% and vehicle-treated subjects. **4b.** Comparison of proportion of subjects achieving ≥2 point improvement in IGA-fissuring severity sub-scores from Baseline to Week 12 between TMB-001 0.05% and vehicle-treated subjects. **5.** Comparison of proportions of subjects achieving ≥ 2-point improvement from Baseline in IGA-scaling and fissuring scores at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing. **6.** Comparison of proportion of subjects who achieve 50% reduction from Baseline in VIIS-scaling scores at Week 24 in all areas with Baseline VIIS score ≥3 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing. **Patient-reported Outcome Endpoints** **7a.** Comparison of proportions of subjects with ≥ 11-point changes from Baseline in IQOL-32 scores at Week 12 between TMB-001 0.05% and vehicle-treated subjects.

	7b. Comparison of proportion of subjects with reduction from Baseline in DLQI or CDLQI ≥4 points at Week 12 between TMB-001 0.05% and vehicle-treated subjects in adult subjects with Baseline scores ≥11 and pediatric subjects with Baseline scores of ≥13. **7c.** Comparison of proportions of subjects with I-NRS and WI-NRS improvement ≥4 points from Baseline in Itch-QoL scores (in subjects with Baseline I-NRS ≥7) at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing. **7d.** Comparison of changes from Baseline in DLQI or CDLQI at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing in adult subjects with Baseline scores ≥11 and pediatric subjects with Baseline scores of ≥13. **7e.** Proportions of subjects with ≥ 11 point change from Baseline in IQoL-32 at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing in adult subjects. • **Safety Endpoints** **8a.** Comparison of proportion of subjects experiencing local skin reactions (LSRs) through Week 12 between TMB-001 0.05% and vehicle-treated subjects. **8b.** Comparison of proportion of subjects experiencing treatment-emergent adverse events (TEAEs) through Week 12 between TMB-001 0.05% and vehicle-treated subjects. **8c.** Comparison of proportion of subjects experiencing LSRs through Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing. **8d**. Comparison of proportion of subjects experiencing TEAEs through Week 24. **9.** Comparison of proportion of subjects demonstrating clinically confirmed allergic contact dermatitis by patch testing through Week 12 between TMB-001 0.05% and vehicle-treated subjects. **Optional Maximal Use Arm** • **Primary Endpoint** Assessment of individual concentrations of isotretinoin, tretinoin, 4-oxo-tretinion and 4-oxo-isotretinoin and change from Baseline. • **Secondary Endpoint** Assessment of individual concentrations of metabolites (isotretinoin, tretinoin and 4-oxo-isotretinoin, 4-oxo-tretinion) and change from Baseline in contemporaneously treated subjects with oral and topical isotretinoin. • **Safety Endpoint** Local safety and tolerability based on dermal irritation scale, physical exam and monitoring of adverse events.
Statistical Methods	Details of all statistical analyses will be described in a separate Statistical Analysis Plan. • **Sample Size Determination** Sample size calculations are based on the results of the Phase IIb study "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". Response rate assumptions for the primary endpoint (proportion of subjects with IGA ≥2-point improvement from Baseline) are 50% in the TMB-001 group and 10% in the vehicle group. A total sample size of 110 subjects randomized in a 2:1 ratio between TMB-001 0.05% and Vehicle will have approximately 90% power to detect a difference of 40% between the treatment groups at the 1% significance level (2-sided). The sample size also covers the proportion of approximately 15% of dropouts and non-evaluable subjects.

- **Primary Efficacy Analysis**

The difference in proportion of subjects achieving IGA treatment success at Week 12 (Visit 6) between the TMB-001 0.05% and vehicle groups will be the primary efficacy 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 improvement (decrease) in severity score as compared to Baseline. Inference will be made by comparing the proportions of treatment successes in the TMB-001 0.05% group vs the vehicle group at Week 12 using the Cochran-Mantel-Haenszel (CMH) test stratified by age (>17, 12-16 and 6-11 years old), and genetic subtype; a two-sided alpha of 0.01 will be used for significance testing.

- **Key Secondary Efficacy Analysis**

The following key secondary efficacy endpoints will be analyzed in a similar fashion as the primary efficacy endpoint based on the initial 12 weeks of treatment (Periods 1 & 2):

- the difference in proportions of subjects who achieve 50% reduction from Baseline in VIIS-scaling scores in all areas with Baseline VIIS score ≥3 between TMB-001 0.05% and vehicle-treated subjects,
- the difference in proportion of subjects with IGA-scaling and fissuring scores of clear or almost clear between TMB-001 0.05% and vehicle-treated subjects,
- the difference in proportion of subjects with ≥2-point improvement from baseline in IGA-scaling severity sub-scores between TMB-001 0.05% and vehicle-treated subjects, and
- the differences in proportions of subjects with ≥4-point improvement from baseline in Worst Itch-QoL scores at Week 12 in subjects with baseline Itch-Numeric Rating Scale (I-NRS) of ≥7 between TMB-001 0.05% and vehicle-treated subjects.

It is important to ensure that reasonable certainty is achieved in the conclusions reached for key secondary endpoints. Therefore, key secondary endpoints will be adjusted for multiple statistical testing through a gatekeeping hierarchical methodology, as follows: statistical significance for the first key secondary endpoint outlined above will be declared only if the primary endpoint has previously reached statistical significance. Subsequent endpoint analyses in the order presented above will be declared significant only if the previous endpoint in order has reached statistical significance. All analyses of key secondary endpoints will be performed at the two-sided alpha-level of 0.01. Missing data for key secondary endpoints will be handled in a similar manner as the primary endpoint.

The changes in continuous endpoints will be analyzed using analysis of covariance (ANCOVA) models with dosing frequency, Baseline scores, age, genetic subtypes, and disease severity as covariates.

- **Safety Analysis**

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 electronic case report forms (eCRFs) will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system. 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. TEAEs and relevant patient years of exposure will be presented, as appropriate. 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 clinically significant laboratory and vital signs values will also be summarized using descriptive statistics. **Optional Maximal Use Arm** The sample size for the Optional Maximal Use arm was requested by the FDA and no formal power calculations were performed. All analyses will be performed on the Maximal Use Population, consisting of all subjects in this study arm that received at least 1 dose of study medication. No statistical analyses are planned, and all data collected will be provided in by-subject listings. If warranted, summary tabulations using descriptive statistics for each visit may be provided.

1.2 Schedule of Assessments (SoA)

Table 1 Schedule of Assessments

	Screening	Baseline[b]							EOS/ ET	Safety follow-up
Visit[a]	**1 (could be split in 2)**	**2**	**3 (remote)**	**4**	**5**	**6[c]**	**7**	**8 (remote)**	**9**	**10[d] (remote)**
	-90 to -7 Days	**Day 0**	**Day 14 (± 1 day)**	**Day 28 (±4 days)**	**Day 56 (±7 days)**	**Day 84 (±7 days)**	**Day 112 (±7 days)**	**Day 140 (±7 days)**	**Day 168 (±7 days)**	**Day 182 (±2 days)**
Informed consent/assent	X									
Genetic testing/confirmation	X									
Inclusion/exclusion criteria	X	X[e]								
Medical history & demographics	X	X (updated)								
Physical examination[f]	X	X[g]				X			X	
Randomization		X[h]				X[i]				
Demonstrate how to apply the study treatment		X								
Clinical laboratory testing[j]	X					X			X	
Concomitant medication	X	X	X	X	X	X	X	X	X	
Vital signs[k]	X	X		X	X	X	X		X	
Serum hCG pregnancy test for WOCBP[l]	X									
Urine pregnancy test[m] for WOCBP[l]		X		X	X	X	X	X	X	
IGA-scaling and fissuring assessment[n]	X	X		X	X	X	X		X	
VIIS-scaling assessment	X	X		X	X	X	X		X	
Record percent of BSA in Treatment Area	X	X				X			X	

	Screening	Baseline[b]							EOS/ ET	Safety follow-up
Visit[a]	**1 (could be split in 2)**	**2**	**3 (remote)**	**4**	**5**	**6[c]**	**7**	**8 (remote)**	**9**	**10[d] (remote)**
	-90 to -7 Days	**Day 0**	**Day 14 (± 1 day)**	**Day 28 (±4 days)**	**Day 56 (±7 days)**	**Day 84 (±7 days)**	**Day 112 (±7 days)**	**Day 140 (±7 days)**	**Day 168 (±7 days)**	**Day 182 (±2 days)**
Itch-Numeric Rating scale[v]		X	X	X	X	X			X	
Age-appropriate Dermatology Life Quality Index[o]		X				X			X	
Ichthyosis Quality of Life-32[p]		X				X			X	
Photography[q]		X		X	X	X			X	
Local skin reactions[r]		X	X	X	X	X	X	X	X	
Subject eDiary: Train (T), Dispense (D), Review (R)		T+D	R	R	R	R	R	R	R	
Study treatment accountability and dispensation to subject[s]		X		X	X	X	X		X	
Adverse events		X	X[t]	X	X	X	X	X	X[u]	X

Abbreviations: BSA= Body Surface Area; CI = Congenital Ichthyosis; EOS = End of Study; ET = Early Termination; hCG = Human Chorionic Gonadotropin; IGA = Investigator's Global Assessment; VIIS = Visual Index for Ichthyosis Severity; WOCBP = Women of Childbearing Potential

a. Visits at Screening, Baseline, V6 and V9 must be performed at the investigational site. Visits 4, 5, and 7 should be performed at the investigational site but can also be performed as telemedicine visits. Visits 3, 8 and 10 are scheduled remote visits.
b. Screening assessments (except for genetic testing) may be performed up to 90 days prior to Visit 2 (Baseline)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 for obtaining genetic confirmation, it can be obtained at any time following consent and with no restriction until Visit 2 (Baseline). The Screening visit may be split into two visits to accommodate the genetics testing first, following by all other screening assessments.
c. Visit 6 (day 84/Week 12) is the EOS visit for subjects who are not eligible to continue maintenance treatment.
d. Subjects at the end of the study or subjects discontinued from the study at any time will be followed-up for additional 2 weeks for AEs.
e. For subjects who require genetic testing, or a washout period related to exclusionary medications, reaffirm these subjects meet all protocol requirements at Visit 2 (Baseline).

f. Examination will include head and neck, dermatologic, cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait assessments. Additional examinations will be conducted at Visit 2 (Baseline) to identify any changes since Screening, at Visit 6 and Visit 9 (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.
g. If there are less than two weeks between Visit 1 (Screening) and Visit 2 (Baseline), the physical examination at the Visit 2 (Baseline) includes only a dermatological assessment.
h. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized at Baseline (2:1 ratio) to either the TMB-001 0.05% or the vehicle treatment group, stratified by age and CI subtype.
i. At Week 12, eligible subjects in the TMB-001 0.05% treatment group will be randomized (1:1 ratio) to either TMB-001 0.05% QD or BID maintenance treatment.
j. Clinical laboratory tests (hematology, clinical chemistry, routine urinalysis) are provided in **Error! Reference source not found.**. Subjects must be fasting (at least 8 hours) for Visit 1 (Screening) and, if possible, for Visit 6 and Visit 9 (EOS). However, if a subject arrives at the clinic for Visit 6 (Week 12) or Visit 9 (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.
k. 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).
l. The term WOCBP is defined in Appendix 4.
m. Urine pregnancy testing will be performed during in-clinic visits and provided to study participants to conduct at home during remote visits. All urine pregnancy tests must have a minimum sensitivity of 25 mIU β-hCG/mL.
n. IGA will be assessed as Scaling and Fissuring Combined Scores and separate Scaling and Fissuring Sub-scores.
o. Subjects ≥16 years will be assessed using the Dermatology Life Quality Index (DLQL) while subjects <16 years will be assessed using the Children's Dermatology Life Quality Index (CDLQI).
p. Ichthyosis Quality of Life Questionnaire (IQoL-32) will be used for subjects >15 years.
q. Photographs will be taken at selected sites (per Photographic Guide provided by Sponsor).
r. For visits performed remotely, local skin reactions will be assessed via the Subject eDiary. Suspected cases of allergic contact dermatitis are to be followed as per Appendix 11.
s. Instruction for study treatment administration will be provided in paper form and will be included in the Subject eDiary.
t. 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/Independent Ethics Committee as an "unanticipated problem" in accordance with local procedures.
u. Any treatment-related AEs that are ongoing at Visit 9 (EOS) must be followed until resolution or stabilization.
v. I-NRS scores will be collected on a daily basis for first 12 weeks

2 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 (Vahlquist 2008). 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, 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 (Takeichi 2016). 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 (Nomura 1995). Autosomal recessive congenital ichthyosis (ARCI), which occurs at a frequency of about one in 100,000 to 300,000, is a member of the non-syndromic autosomal recessive CI group which manifests itself clinically as hyperkeratosis and dry, scaling skin across the entire body (Vahlquist 2014); pathogenesis is related to a severely disturbed barrier function due either abnormal corneocytes or to a defective deposition of stratum corneum lipids and can be caused by truncation or missense mutations in the gene encoding keratinocyte transglutaminase type 1 (TGM1) (Vahlquist 2008, Vahlquist 2014).

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 (Digiovanna 2013). Isotretinoin is structurally and pharmacologically related to vitamin A, which regulates epithelial cell growth and differentiation (GlaxoSmithKline Australia Pty Ltd 2013). 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 (Layton 2009). 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 (Layton 2009). 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 (Blaner 2001). Thus, isotretinoin's broader range of activity compared to other retinoids makes it advantageous for clinical development.

Oral isotretinoin (Accutane®) capsules were first approved by the United States (US) Food and Drug Administration (FDA) as treatment for severe recalcitrant nodular acne in 1982 (Roche Laboratories Inc 1982). 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 (e.g., reductions and/or drug holidays) and additional symptomatic therapy (e.g., 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 (GlaxoSmithKline Australia Pty Ltd 2013, GlaxoSmithKline UK Limited 2014). Another topical formulation, isotretinoin cream, 0.1%, has also been studied in various indications including ichthyosis and other disorders of keratinization (Burge 1995, Steijlen 1993) and acne vulgaris (Chalker 1987, Dominguez 1998, Hughes 1992, Ioannides 2002, Jensen 1991).

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 (e.g., 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%) formulation of isotretinoin called TMB-001 (previously PAT-001) (isotretinoin) ointment for the treatment of CI, including RXLI and ARCI subtypes. An initial Phase IIa study in subjects aged ≥12 years has shown favorable efficacy after treatment with TMB-001 0.1% ointment. A subsequent Phase IIb study with TMB-001 0.05% and 0.1% ointment demonstrated reduced clinical signs of CI in subjects aged ≥9 years, with significant improvement of Visual Index for Ichthyosis Severity (VIIS)-scaling and the Investigator Global Assessment (IGA) scaling/fissuring severity score.

The purpose of this Phase III study is to investigate the efficacy and safety of topically applied TMB-001 0.05% in subjects aged ≥6 years with RXLI or ARCI while the Optional Maximal Use arm will evaluate systemic exposure and safety.

2.2 Background

CI is a large, heterogeneous family of inherited skin disorders of cornification resulting from an abnormality of skin keratinization (Vahlquist 2008).

The management of CI is a life-long endeavor, which remains largely symptomatic (i.e., emollients with or without keratolytics) and commonly focused on reducing scaling and/or skin lubrication with both systemic and topical treatments (Vahlquist 2008). 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 (e.g., 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 (Digiovanna 2013); 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 decrease hyperkeratinization (Vahlquist 2008, Digiovanna 2013). For the treatment of CI, it would be desirable to have a topical formulation of isotretinoin, such as TMB-001, Timber's proprietary isotretinoin ointment, 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.

An initial Phase IIa, multicenter study in subjects aged ≥12 years 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.

In a subsequent parallel, double-blind, vehicle-controlled Phase IIb study in subjects aged ≥9 years with confirmed CI, 10%–90% of total body surface area (BSA) affected, subjects were randomized (1:1:1 ratio) to TMB-001 0.05% (n=11), TMB-001 0.1% (n=10) or Vehicle (n=12) twice daily (BID) for 12 weeks. Key efficacy endpoints at 12 weeks were the proportion of subjects with a ≥50% reduction compared with Baseline in VIIS-scaling (VIIS-50); and the proportion of subjects with ≥2-grade reduction in IGA-scaling and fissuring severity score vs Baseline. Adverse events (AEs) and local skin reactions (LSRs) were also assessed. The mean age of the subjects was 34.5 years; 55% and 45% of the enrolled subjects had lamellar ichthyosis (LI) and RXLI subtypes of CI, respectively. Overall, 64% and 40% of Intention-to-treat (ITT) subjects treated with TMB-001 0.05% and 0.1%, respectively achieved VIIS-50 compared with 33% treated with vehicle (nominal P=0.17 for TMB-001 0.05% vs vehicle). Median time (ITT) to VIIS-50 achievement was 28.0 days for TMB-001 0.05% and 54.0 days for TMB-001 0.1% compared with 63.5 days for Vehicle (P=0.02 for 0.05%). Improvement of ≥2-grade IGA score was observed in 55% of TMB-001 0.05% and 40% of TMB-001 0.1% compared with 8% for Vehicle (nominal P=0.02 for 0.05%). Most LSRs were mild or moderate in severity and occurred at Weeks 2 and 4. By Week 12, burning/stinging and erythema were reported in 18% and 36% of subjects receiving TMB-001 0.05% and TMB-001 0.1%, respectively. No subjects reported edema and 18% and 30% of subjects reported mild skin erosions for TMB-001 0.05% and 0.1%, respectively. No hospitalizations, serious adverse events (SAEs) or deaths were observed.

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 (e.g., 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 subjects with non-erythrodermic LI, 2/2 subjects with Darier's disease, and 0/1 subjects with autosomal dominant ichthyosis vulgaris). However, this clinical improvement was accompanied by local skin irritation (e.g., itchy erythema) in responders, and dose modifications were often prescribed to mitigate such effects (Steijlen 1993). 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 BID as tolerated) in 50% (6/12) of subjects 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 (Vahlquist 2008, Digiovanna 2013).

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

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

Systemic exposure is expected to be low given the route of topical administration. In minipigs receiving once daily dermal applications of TMB-001 ointment for 90 days at concentrations of 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 IIa clinical study of subjects with CI involving 12% BSA, where TMB-001 0.1% and 0.2% ointment concentrations were tested, the serum concentrations of isotretinoin and tretinoin were measured for 12 weeks (n=5). 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.

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

2.3.1 Risk/ burden in minors

The expected risk/burden in minors is expected to be similar to subjects over the age of 18 years. The current study proposes similar amounts of investigational product applied/m^2, regardless of age. The safety profile achieved in minor subjects in the Phase 2A and Phase 2B programs was similar to that of older subjects. Local toxicity and skin reactions will be consistently evaluated throughout the trial in these minor subjects. Risk to children in this program should be compared with lack of on-label alternative products for treatment of congenital ichthyosis in children and adolescents; for example, acitretin is not approved for use in children with congenital ichthyosis in the European Union.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy Objective	**Primary Efficacy Endpoint**
To ascertain the efficacy of TMB-001 0.05% topical ointment as a treatment for CI compared with Vehicle during a 12-week treatment.	Comparison of proportions of subjects with ≥2-point changes from Baseline in IGA-scaling and fissuring scores in the Treatment Area at Week 12 between TMB-001 0.05% and vehicle-treated subjects.
Key Secondary Efficacy Objectives	**Key Secondary Efficacy Endpoints**
1. To ascertain the efficacy of TMB-001 0.05% topical ointment at Week 12 using the VIIS-50 scaling score.	**1.** Comparison of proportion of subjects who achieve 50% reduction from Baseline in VIIS-scaling scores at Week 12 in all areas with Baseline VIIS score ≥3 between TMB-001 0.05% and vehicle-treated subjects.
2. To ascertain the efficacy of TMB-001 0.05% topical ointment at Week 12 using the IGA-scaling and fissuring scores.	**2a.** Comparison of proportion of subjects with IGA-scaling and fissuring scores of clear or almost clear at Week 12 between TMB-001 0.05% and vehicle-treated subjects. **2b.** Comparison of proportions of subjects who achieve IGA-scaling severity sub-score improvement ≥ 2-points from Baseline to Week 12 between TMB-001 0.05% and vehicle-treated subjects.
3. To evaluate the effect of TMB-001 0.05% topical ointment on subject Itch-QoL scores at Week 12 in subjects with baseline Itch-Numeric Rating Scale (I-NRS) of ≥7	**3.** Comparison of proportion of subjects with ≥4-point improvement from baseline in Worst Itch-QoL scores at Week 12 in subjects with baseline Itch-Numeric Rating Scale (I-NRS) of ≥7 between TMB-001 0.05% and vehicle-treated subjects. .
Other Secondary Efficacy Objectives	**Other Secondary Efficacy Endpoints**
4. To ascertain the efficacy of TMB-001 0.05% topical ointment at Week 12 using different levels of VIIS-scaling and IGA-scaling and fissuring scores.	**4a.** Comparison of proportion of subjects who achieve 25% reduction from Baseline in VIIS-scaling scores at Week 12 in all areas with Baseline VIIS score ≥3 between TMB-001 0.05% and vehicle-treated subjects. **4b.** Assessment of proportion of subjects with ≥ 2-point improvement from baseline to Week 12 in IGA fissuring severity sub-scores between TMB-001 0.05% and vehicle-treated subjects.
5 To determine optimal maintenance therapy with TMB-001 0.05% topical ointment using the IGA scaling and fissuring scores.	**5.** Comparison of proportions of subjects with ≥2-point changes from Baseline in IGA-scaling and fissuring scores at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing.

6. To determine optimal maintenance therapy with TMB-001 0.05% topical ointment using VIIS-scaling scores.	**6.** Comparison of proportion of subjects who achieve 50% reduction from Baseline in VIIS-scaling scores at Week 24 in all areas with Baseline VIIS score ≥3 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing.
Patient-reported Outcome Measures	**Patient-reported Outcome Endpoints**
7. To evaluate the effect of TMB-001 0.05% topical ointment on subject QoL during the 12-week treatment period and subsequent 12-week maintenance period.	**7a.** Comparison of proportions of subjects with ≥11-point changes from Baseline in IQOL-32 scores at Week 12 between TMB-001 0.05% and vehicle-treated subjects. **7b.** Comparison of proportion of subjects with reduction from Baseline in DLQI or CDLQI ≥4 points at Week 12 between TMB-001 0.05% and vehicle-treated subjects in adult subjects with Baseline scores ≥11 and pediatric subjects with Baseline scores of ≥13. **7c.** Comparison of proportion of subjects with ≥4-point changes from Baseline in Itch-QoL scores (in subjects with Baseline I-NRS ≥7) at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing. **7d.** Comparison of proportion of subjects with ≥4-point changes from Baseline in DLQI or CDLQI at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing in adult subjects with Baseline scores ≥11 and pediatric subjects with Baseline scores of ≥13. **7e.** Comparison of proportion of subjects with ≥11-point changes from Baseline in IQoL-32 at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing in adult subjects.
Safety Objectives	**Safety Endpoints**
8. To investigate the safety of topically applied TMB-001 0.05% ointment. **9.** To evaluate incidence of suspected allergic contact dermatitis	**8a.** Comparison of proportion of subjects experiencing LSRs through Week 12 between TMB-001 0.05% and vehicle-treated subjects. **8b.** Comparison of proportion of subjects experiencing TEAEs through Week 12 between TMB-001 0.05% and vehicle-treated subjects. **8c.** Comparison of proportion of subjects experiencing LSRs through Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing. **8d**. Comparison of proportion of subjects experiencing TEAEs through Week 24. **9.** Comparison of proportion of subjects demonstrating clinically confirmed allergic contact dermatitis by patch testing through Week 12 between TMB-001 0.05% and vehicle-treated subjects.

Abbreviations: BID = Twice Daily; CDLQI = Children's Dermatology Life Quality Index; CI = Congenital Ichthyosis; DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; I-NRS = Itch-Numeric Rating Scale; IQoL = Ichthyosis Quality of Life; QD = Once a Day; LSR = Local Skin Reaction; QoL = Quality of Life; TEAE = Treatment-emergent Adverse Events; VIIS = Visual Index for Ichthyosis Severity.

Table 3 Objectives and Endpoints – Optional Maximal Use Arm

Objectives	**Endpoints**
Primary Objective	**Primary Endpoint**
To determine systemic exposure of isotretinoin and metabolites after single or multiple applications of TMB-001 0.05% ointment in subjects with X-linked and autosomal recessive CI.	Assessment of individual concentrations of isotretinoin, tretinoin 4-oxo-tretinion and 4-oxo-isotretinoin and change from Baseline.
Secondary Objective	**Secondary Endpoint**
To compare systemic exposure of isotretinoin and metabolites after single or multiple applications of TMB-001 0.05% ointment cross-trial for PK parameters obtained for oral isotretinoin (single dose 80 mg) in healthy volunteers.	Assessment of individual concentrations of metabolites (isotretinoin, tretinoin and 4-oxo-isotretinoin, 4-oxo-tretinion) and change from Baseline in contemporaneously treated subjects with oral and topical isotretinoin.
Safety Objective	**Safety Endpoint**
To assess local safety and tolerability of TMB-001 0.05% ointment in adult and pediatric subjects for up to 12 weeks.	Local safety and tolerability based on dermal irritation scale, physical exam and monitoring of AEs.

Abbreviations: AE = Adverse Event; CI = Congenital Ichthyosis; PK = Pharmacokinetic

4 STUDY DESIGN

4.1 Overall Design

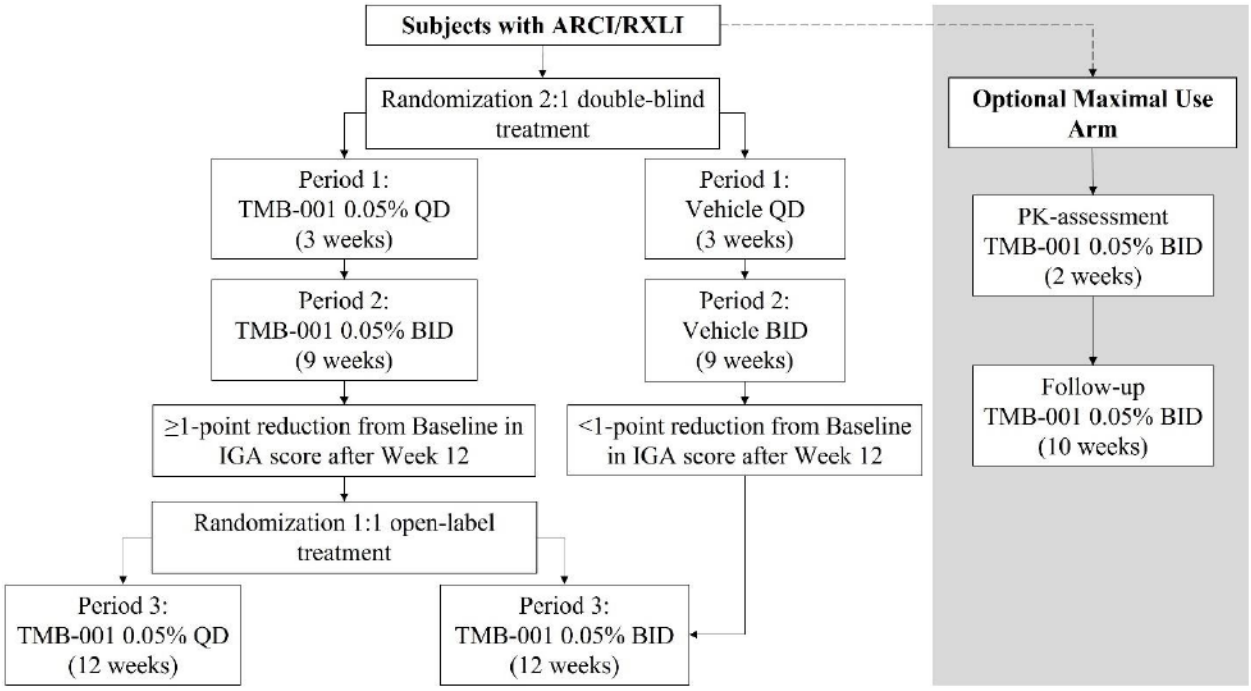
This is a randomized, double-blind and vehicle-controlled Phase III study to evaluate the safety and efficacy of topical TMB-001 0.05% ointment for the treatment of CI in subjects with either the RXLI or ARCI subtypes.

In addition, a subset of preselected centers will recruit subjects in parallel with either the RXLI or ARCI subtypes for enrollment into an Optional Maximal Use arm for evaluation of the systemic exposure and safety of topical TMB-001 0.05% ointment for the treatment of CI.

Protocol Sections 1 through 8 are applicable for both the Phase III study and the Optional Maximal Use arm, unless otherwise stated. Aspects that are specific to the Optional Maximal Use arm are described in Section 9.

The overall study design is presented in Figure 1.

Figure 1 Overall Study Schema



Abbreviations: ARCI = Autosomal Recessive Congenital Ichthyosis; BID = Twice Daily; IGA = Investigator's Global Assessment; PK = Pharmacokinetic; QD = Once a Day; RXLI = Recessive X-linked Ichthyosis

The Phase III Study is designed in three periods (Figure 1):

- **Period 1 – Induction (3 weeks):**
  At the beginning of the 3-week Induction Period, eligible subjects will be randomized (2:1 ratio) to either TMB-001 0.05% once-a-day (QD) or Vehicle QD treatment, with use of mandatory standardized bland emollient (Cetaphil™) provided by the Sponsor.
- **Period 2 – Treatment (9 weeks):**
  The dosing frequency in the 9-week treatment period will be increased in each treatment group to TMB-001 0.05% BID or Vehicle BID. Mandatory bland emollient will be discontinued.
- **Period 3 – Maintenance (12 weeks):**
  At Week 12, eligible subjects in the TMB-001 treatment group will be randomized (1:1 ratio) to an open-label treatment with TMB-001 0.05% BID or TMB-001 0.05% QD. To be eligible, subjects must have achieved a ≥1-point reduction in IGA score from Baseline. Subjects with less than a 1-point reduction in IGA score from Baseline will be discontinued from the study.

  Vehicle-treated subjects who achieved <1-point reduction in IGA score from Baseline are eligible to cross over to the TMB-001 0.05% BID treatment group. Subjects with a ≥1-point reduction in IGA score from Baseline will be discontinued from the study.

Subjects at the end of the study or subjects discontinued from the study at any time will be followed-up for additional 2 weeks for AEs.

Each subject will participate in the study for approximately 36 weeks (including up to a 90-day screening period).

The study will be conducted in approximately 30-40 study centers from United States of America, Canada and several European countries.

4.2 Discussion of Study Design

This is a multicenter, randomized, double-blind, vehicle-controlled Phase III study to evaluate the efficacy and safety of TMB-001 0.05% topical ointment in the treatment of CI. Subjects will be selected according to predefined entry criteria. The study treatment duration is 24 weeks and expected to be sufficient to show a treatment effect.

Isotretinoin is an approved active pharmacological ingredient with a long history of safe use in humans. However, isotretinoin is a known teratogen with an extremely high risk for severe birth defects if pregnancy occur while taking oral isotretinoin in any amount, even for a short period of time. Therefore oral, systemic isotretinoin requires an iPLEDGE program (iPLEDGE 2012), which is a risk management distribution program mandated by the FDA. To minimize pregnancy risks, WOCBP will only be enrolled if they agree to use highly effective methods of contraception consistently and correctly as described in Table 18 and undergo regular pregnancy testing (Section 8.3.5).

To minimize bias, subjects will be blinded and randomly assigned to treatment with TMB-001 0.05% or Vehicle (Figure 1), additionally subjects who had previously been treated with TMB-001 will be excluded from this study but can be enrolled in the optional Maximal Use arm (in a subset of preselected centers). The use of a vehicle control group is consistent with FDA's standard for generating valid scientific evidence to definitively support safety and efficacy. The vehicle group accounts for the effects of treatment that do not depend on the test treatment. The study is designed to mitigate safety risks by using an initial 2:1 randomization (active treatment to vehicle), along with frequent clinic visits over the 12-week treatment period. The subsequent 1:1 randomization of eligible TMB-001 0.05% treated subjects to two dosing regimen (QD or BID) allows for assessment of the optimal TMB-001 0.05% maintenance therapy as well as provides additional safety data for 12 weeks. The cross-over of eligible subjects from the vehicle control group will also provide additional safety data.

Overall, the study design is considered to be scientifically robust and clinically relevant for evaluating TMB-001 0.05% treatment for the safe and effective treatment of CI.

The design of the Optional Maximal Use arm is discussed in Section 9.1.1

4.3 Justification for Dose

The concentration of TMB-001 0.05% ointment chosen for this study is based on the formulation integrity, the safety and efficacy data from the prior Phase IIa and Phase IIb clinical studies, specific laboratory animal toxicology studies performed by the Sponsor, and a review of the published safety data for isotretinoin. The dose to be applied, TMB-001 0.05%, is based on the potential for therapeutic benefit balanced with the safety risk from the Phase IIb study (Section 2.1).

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 for subjects who do not qualify for maintenance therapy, Visit 9 for subjects who qualify for maintenance therapy) per the SoA (Table 1). The end of the study is defined as the date of the last visit of the last subject in the study.

The end of study definition of the Optional Maximal Use arm is described in Section 9.1.2.

5 STUDY POPULATION

The following inclusion/exclusion criteria will be used at Visit 1 (Screening) and Visit 2 (Baseline) to determine eligibility for entry into the Phase III study and the Optional Maximal Use arm (Sections 5.1 and 5.2).

5.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation:

1. Subject is male or female, 6 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 2 acceptable forms of birth control. WOCBP must have a negative serum pregnancy test at screening and 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 4. 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 of birth control for the duration of the study.
4. Subject has clinical diagnosis of CI based upon phenotype and has a genetic confirmation of either ARCI (including but not exclusively transglutaminase 1-deficient, ALOX-12B) or RXLI (e.g., deletion of steroid sulfatase gene) subtypes of CI. Other genetically confirmed ARCI mutations can potentially be enrolled as long as the phenotype is consistent with ARCI and the other inclusion criteria are met, as determined by the Investigator (see Appendix 5).
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).
    - **For the Optional Maximal Use arm:** The amount of CI affected skin in the Treatment Area at Baseline will be between a minimum of 75% and maximum of 90% of the total BSA.
6. Documented history of moderate to severe disease at Screening. Subject's designated VIIS Assessment Areas at Baseline (**not applicable for Optional Maximal Use arm**) 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 kneecap), 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's IGA score in the Treatment Area at Baseline must be 3 or more.
8. 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.
9. 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 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 exclusion 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 (e.g., atopic dermatitis) unrelated to ichthyosis.
3. Subject has phenotypic clinical presentation and/or genetic abnormality consistent with non-lamellar type or syndromic ichthyoses (including but not exclusively KRT1, KRT10, KRT2, GJB3, GJB4, CDSN)
4. Subject, in the Treatment Areas, has used: (*a*) any topical prescription or over-the-counter (OTC) 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, in the Treatment Areas, has used TMB-001 in the past or oral isotretinoin in the past 12 months (**not applicable for Optional Maximal Use arm**).
6. Subject has used any topical products in the Treatment Areas, including bland emollients, on Visit 2 (Baseline).
7. Subject has used ultraviolet (UV) treatment within 4 weeks prior to Visit 2 (Baseline).
8. 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.*

9. Subject is immunosuppressed (e.g., 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 or five half-lives prior to Visit 2 (Baseline).
13. Subject has lesions suspicious for skin cancer (if skin cancer is not ruled out by biopsy), a known personal or immediate family history of squamous cell carcinoma of the skin or melanoma or untreated skin cancers within the Treatment 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 x Upper Limit of Normal (ULN) and/or creatinine >1.5 x 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 (e.g., 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.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in either the Phase III study or the Optional Maximal Use arm but do not meet the eligibility criteria. 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 SAE will be collected and recorded in the electronic data capture system.

Individuals who do not meet the criteria for participation in the studies (screen failure) may be rescreened for the following circumstances:

- Subjects who fail to complete their washout in time for their scheduled Visit 2 (Baseline) can be allowed to continue the washout and Visit 2 may be rescheduled.

- Subjects who have a clinically non-significant out-of-range laboratory result may be rescreened one time.

Any subject who is rescreened is required to have a new informed consent form (ICF)/assent.

6 STUDY TREATMENT

6.1 Study Treatment(s) Administered

6.1.1 Treatment Area

The Treatment Area for each subject is defined as 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, inner thighs near genitalia and genitalia] are possible treatment areas).

6.1.2 Treatment Administration

Treatments administered during the Phase III study, including frequencies and durations are presented below in Table 5. Study medication will be applied to up to 90% of the BSA. Prior to randomization, the location of the CI to be treated and the percent BSA with CI in the Treatment Area (see Section 8.2.3) will be recorded.

6.1.2.1 Maximum Daily Dose

The approximate maximum daily doses expected are outlined below in Table 4. As study medication can be applied to up to 90% BSA twice daily, these parameters were calculated to estimate the maximum daily doses in pediatric and adult subjects.

Table 4 Maximum Daily Dose

	Height	Weight	BSA in m2	90% BSA	Amount of Isotretinoin applied daily (TMB-001 0.05% at BID dosing)	Amount of drug/m^2 applied daily with BID dosing
Average 6 year old	110cm	20.3kg	0.7799m^2	0.7019m^2	0.013g a day	0.019g/m^2
Average adult male	179cm	71.9kg	1.9002m^2	1.7101m^2	0.034g a day	0.020g/m^2

Treatment administration specific to the Optional Maximal Use arm is described in Section 9.2.

Table 5 Treatment Administration

Study Period	Treatment Administration
Study Period 1 (Induction)	• TMB-001, 0.05%, QD for 3 weeks along with mandatory standardized bland emollient (Cetaphil™) provided by Sponsor • Vehicle ointment (Control) QD for 3 weeks along with mandatory standardized bland emollient (Cetaphil™) provided by Sponsor
Study Period 2 (Treatment)	• TMB-001 0.05% ointment BID for 9 weeks without mandatory emollients • Vehicle ointment BID for 9 weeks without mandatory emollients
Study Period 3 (Maintenance)	• TMB-001, 0.05%, QD or BID from Week 12 to 24 without mandatory emollients

Abbreviations: BSA = Body Surface Area; BID = Twice Daily; QD = Once a day; VIIS = Visual Index for Ichthyosis Severity

When applied BID, the study medication should be administered ideally once in the morning and once in the evening, but at least 6 hours apart. When applied QD, the study medication can be applied at any time of the day provided applications are separated by at least 12 hours.

Per protocol amounts of study medication to be applied based on subject's percent BSA are indicated in the Subject and Site Instruction Sheet as well as in the Subject electronic Diary (eDiary). 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 eDiary. Product application will be clearly demonstrated by the Investigator or a designated healthcare professional at the Baseline visit, and the subject and parent/guardian (if applicable) will be provided with a Subject Instruction Sheet.

Under all circumstances when emollients are mandated by protocol or required for treatment of LSRs, emollients should be applied either 3-5 hours prior to or following application of TMB-001 0.05% or Vehicle as applicable. Emollients under all circumstances should be withheld for 24 hours prior to any scheduled efficacy visits as outlined in the SoA (Table 1 and Table 13).

Study treatment details are provided in Table 6. The vehicle ointment contains only the inactive ingredients and color additive so that the active and vehicle formulations are indistinguishable.

Table 6 Study Treatments

Study Treatment Name:	TMB-001 0.05%	Vehicle
Dosage Formulation:	Ointment	Ointment
Unit Dose Strength(s)/Dosage Level(s):	0.05%	Not applicable
Route of Administration	Topical	Topical
Dosing Instructions:	Once a day (QD) for first 3 weeks then twice a day (BID) (morning and evening) for next 9 weeks, then QD or BID for 12 weeks (depending on randomization)	QD for first 3 weeks then BID (morning and evening) for next 9 weeks

Study Treatment Name:	TMB-001 0.05%	Vehicle
Packaging and Labeling	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.
Storage Temperature	Store at 36°F to 46°F (2°C to 8°C) until assigned to study participant. Once assigned, 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).	Store at 36°F to 46°F (2°C to 8°C) until assigned to study participant. Once assigned, 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).
Manufacturer	[redacted], USA	[redacted], USA

Note: Subjects in both the TMB-001 0.05% treatment and the vehicle treatment group will apply a bland emollient (Cetaphil™ Moisturizing Lotion) provided by the Sponsor during Study Period 1 (see Section 4.1).

6.2 Preparation/Handling/Storage/Accountability

TMB-001 0.05% 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.

The study treatment will be shipped directly to the study site. The Investigator or designee must confirm that appropriate temperature conditions (Table 6) have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

At study time points indicated in the SoA (Table 1 and Table 13), subjects will be given tubes of study treatment for dosing at home, sufficient for dosing between clinical visits. The dispensed tubes must be returned to the study center during the next in clinic visit where study treatment accountability will be performed by the site staff. The tubes will be weighed periodically as detailed in the IP Handling Guidelines.

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 treatments are provided in the Investigator Study Binder.

6.3 Randomization

Subjects enrolled in the study who meet all inclusion criteria and none of the exclusion criteria will be randomized at Baseline (2:1 ratio) to either the TMB-001 0.05% or the vehicle treatment

group, stratified by age, and CI sub-type. At Week 12, eligible subjects in the TMB-001 0.05% treatment group will be randomized (1:1 ratio) to either TMB-001 0.05% QD or BID maintenance treatment (Figure 1).

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.

The Optional Maximal Use arm is open-label and does not require randomization.

6.3.1 Blinding and Unblinding

In the double-blind Induction and Treatment Period (Study Periods 1 and 2) of the study, all personnel involved, i.e., physicians, site staff, participants and Sponsor 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 7.1. Any departures from the intended regimen must be recorded in the eCRF.

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

6.5 Concomitant Therapy

Prohibited medication and treatments including the washout periods are summarized in Table 7.

- Non-petrolatum bland emollients[a] and OTC low potency hydrocortisone (e.g., 1% cream) may only be used in the event of severe discomfort (e.g., burning/erythema/itch) (after Week 3 in the Phase III study and during the entire time in the Optional Maximal Use arm) and if it is the opinion of the Investigator that a drug interruption (per Section 7.1)

[a] Subjects enrolled in the study will use mandatory bland emollients during the Induction Period (1-3 weeks). After the Induction Period, bland emollients will be prohibited for these subjects until the EOS visit. Subjects enrolled into the Optional Maximal Use arm should discontinue the use of bland emollients at Visit 2 (Baseline).

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 treatments 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.
- Subjects should limit exposure to UV via sunlight and avoid tanning beds.

Table 7 Prohibited Medication and Treatments Including Time Point of Discontinuation

Prohibited Medication	**Time Point of Discontinuation**
• Topical retinoids • Topical prescription or over-the-counter therapies	2 weeks before Visit 2 (Baseline)
• Keratolytics • Topical corticosteroids	5 days before Visit 2 (Baseline)
• Bland emollients	• Visit 2 (Baseline) – **for Optional Maximal Use arm** • Visit 4 (Week 4) – **for Phase III study**
• Over-the-counter low potency hydrocortisone	Visit 2 (Baseline)
Prohibited Systemic Treatment	**Time Point of Discontinuation**
• Systemic retinoids	
o Isotretinoin	• 12 weeks before Visit 2 (Baseline) – **for Optional Maximal Use arm** • 1 year before Visit 2 (Baseline) – **for Phase III study**
o Acitretin	• 3 months before Visit 2 (Baseline)
• Vitamin A supplements • St. John's Wort • Other therapies intended for CI or may improve CI	4 weeks before Visit 2 (Baseline)
• Immunosuppressive drugs (e.g., systemic corticosteroids)	2 weeks before Visit 2 (Baseline)
Other	**Time Point of Discontinuation**
• Ultraviolet treatment	4 weeks before Visit 2 (Baseline)

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 OTC 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.

7 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

A list of the data to be collected at the time of treatment discontinuation, follow-up and for any further evaluations that need to be completed is given in the SoA (Table 1 and Table 13).

7.1 Temporary Discontinuation (Drug Interruption/Reduction)

A treatment interruption scheme will be allowed if a subject experiences skin AEs or LSRs during the study. Any subjects with an LSR (especially early during treatment) will be encouraged to continue with their study treatment since transient skin irritation is known to develop with topical retinoids, but LSRs may also develop due to the vehicle formulation or other reasons.

As the study medication will be applied to multiple areas of the body (Treatment Area), it is likely that skin LSRs/AEs may only occur in certain body parts or be more severe in certain body parts. Therefore, actions taken to the study medication do not need to be consistent in the Treatment Area. Proper recording in the eCRF of the body part(s) affected and action taken will be important to document all drug interruptions/reductions. It is desirable to make every effort to maintain subjects in the study to allow adequate assessment of efficacy and safety.

The schedule below (Table 8) outlines the recommended action taken to the study medication based on severity and frequency of the LSR/AE. Deviations to this must be reviewed with the Medical Monitor. The most current NIH Common Terminology Criteria Adverse Events (CTCAE), specifically the subgroups of Skin and Subcutaneous Tissue Disorders and grading system will be used to define severity of LSRs/ adverse events.

Table 8 Recommended Actions taken at AE/LSR Occurrence

	Severity	Action to Study Medication
First and Second Occurrence	Grade 1	If currently dosing twice daily (BID), reduce frequency to once a day (QD) in specific affected area(s) for 3 days. Once resolved, reinitiate BID dosing. If currently dosing QD, discontinue for 3 days in specific affected area(s). Once resolved, reinitiate QD dosing.
	Grade 2	Discontinue use in specific affected area(s) for at least 3 days, no more than 7 days. Once resolved, reinitiate to QD dosing for 7 days. If tolerated, then increase to BID dosing.
	Grade 3	Discontinue use in specific affected area(s) for at least 7 days, no more than 14 days. Once resolved, reinitiate at QD dosing. If no resolution after 14 days, permanently discontinue use in the specific area(s).

	Severity	Action to Study Medication
Third Occurrence	Grade 1	Reduce frequency to QD in specific affected area(s) for 3 days. Once resolved, reinitiate BID dosing.
	Grade 2	Discontinue use in specific affected area(s) for at least 3 days, no more than 7 days. Once resolved, reinitiate to QD dosing for 7 days. If tolerated, then increase to BID dosing.
	Grade 3	Permanently discontinue study medication in any/all affected areas
Fourth Occurrence	Grades 1-3	Investigator and subject discuss regarding permanently discontinuing study medication in any/all affected areas.

In addition to modifying the study medication usage, treatment with non-petrolatum bland emollients (e.g., Cetaphil™) and/or low dose topical corticosteroid, could be introduced at Investigator discretion. These treatments should be stopped once the LSR has resolved, and the study medication reinitiated as per the table.

7.2 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:

- his/her own or parent/legal guardian request
- or he/she may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (e.g., withdrawal of informed consent).

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 Table 1 and Table 13 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. Subjects discontinued from the study at any time will be followed-up for additional 2 weeks for AEs.

The discontinuation of specific study centers or of the study are handled as detailed in Appendix 1.

7.3 Lost to Follow-Up

A subject will be considered lost to follow-up if he/she fails to return for scheduled visits without notifying the site 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.

7.4 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 8.4.3 and Appendix 4.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing for both the study and the Optional Maximal Use arm are summarized in the SoA (Table 1 and Table 13). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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 will not be considered for this study and assessments/procedures not completed as per protocol will be recorded as deviations. Acute 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 General Study Assessments

8.1.1 Informed Consent/Assent

A complete description of the study will be presented to the subject or parent/legal guardian of each potential subject (for subjects aged <18 years) and signed and dated. Informed consent will be obtained before any study-specific procedures are performed. The detailed informed consent process is described in Appendix 1.

8.1.2 Genetic Testing

To be eligible for the study, subjects must have moderate to severe CI that has been genetically confirmed to be of either the ARCI or RXLI subtype. For ARCI subjects, enrollment is not limited to transglutaminase 1 mutations. Other genetically confirmed ARCI- mutations with a lamellar phenotype can potentially be enrolled (Appendix 5) as long as the phenotype is consistent with ARCI and the other inclusion criteria are met, as determined by the Investigator.

Genetic testing/confirmation will be performed at the time points designated in the SoA (Table 1 and Table 13).

Subjects who already have had a genetic test documenting ARCI 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 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. Genetic testing will consist of a buccal swab that is sent to one of two central laboratories depending on the subject's geographic location (North America vs Europe). The swab can either be obtained at the clinical site or by the subject at home. Instructions on how to complete the swab are included in the kit. The test will only report on genes associated with CI and results will be sent directly to the Investigator.

8.1.3 Demographics/Medical History

Medical history and demographic data including the subject's gender, date of birth, and concomitant medication use will be obtained for all subjects during Screening.

The medical history should be updated at Visit 2 (Baseline) prior to randomization (Phase III study) or first dose of study medication (Optional Maximal Use arm) to assess continued study eligibility and adherence to final inclusion/exclusion criteria. This medical history update includes a review for changes from Screening as well as a review of the patient's recent medication use to assess whether any changes have occurred since the previous visit.

8.2 Efficacy Assessments

Study procedures and their timing are summarized in the SoA (Table 1). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.2.1 Investigator's Global Assessment (IGA)

The primary efficacy assessment will be performed using the IGA (combined scaling and fissuring). For secondary efficacy assessments, scaling and fissuring will be evaluated separately using the respective sub-scores (Table 9).

Subject IGA scores will be assessed in the entire Treatment Area at the time points designated in the SoA (Table 1). 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/or 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/or fissuring. The IGA will be assessed using the 5-point scale as shown in Table 9. The same assessor should be evaluating the IGA scores at Baseline and throughout the study for each individual subject.

Table 9 Investigator's Global Assessment Score (5-Point Scale)

Score	Category	Scaling and Fissuring Combined Scores	Scaling Sub-score	Fissuring Sub-score
0	Clear	No scaling and no roughness, no fissuring	No scaling, no roughness	No fissuring
1	Almost Clear	Occasional fine scales, hardly palpable roughness (mostly smooth), rare fissuring and/or clinically insignificant fissuring severity	Occasional fine scales, hardly palpable roughness (mostly smooth)	Rare fissuring and/or clinically insignificant fissuring severity
2	Mild	Small and fine scales predominate, no more than a few large scales, mild roughness on palpation, few fissures with minimal pain or	Small and fine scales predominate, no more than a few large scales,	Few fissures with minimal pain or symptoms that impair patient ADLs and/or

Score	Category	Scaling and Fissuring Combined Scores	Scaling Sub-score	Fissuring Sub-score
		symptoms that impair patient ADLand/or minimally clinically significant fissuring severity	mild roughness on palpation	minimally clinically significant fissuring severity
3	Moderate	Large rather thick scales predominate, coarse roughness on palpation, multiple fissures with possible pain or symptoms that somewhat impair ADLs and/or clinically significant fissuring severity	Large rather thick scales predominate, coarse roughness on palpation	Multiple fissures with possible pain or symptoms that somewhat impair ADLs and/or clinically significant fissuring severity
4	Severe	Large coalescent scales dominate, sharp edges on palpation with plate-like hyperkeratosis, numerous fissures and/or pain and symptoms that impair ADLs and/or very clinically significant fissuring severity	Large coalescent scales dominate, sharp edges on palpation with plate-like hyperkeratosis	Numerous fissures and/or pain and symptoms that impair ADLs and/or very clinically significant fissuring severity

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

- On-site visual inspection
- Optional remote instead of on-site visits due to the ongoing Coronavirus Disease 2019 (COVID-19) pandemic comprised of both photographs and tele-medicine utilizing synchronous videoconferencing technology. The severity score at each visit will be based on information gathered from both sources to yield one score but remote evaluations cannot be used at Visits 1, 2, 6 or 9 unless there is a documented physical restriction to travel, such as COVID-19. All efforts will be made to have all visits on-site, the location of all assessments will be noted in the eCRF.

8.2.2 Visual Index for Ichthyosis Severity (VIIS) – Scaling

One of the key secondary efficacy assessments will be performed using the VIIS-scaling score. Subject VIIS-scaling scores will be assessed at the time points designated in the SoA (Table 1). Four VIIS Assessment Areas are 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 kneecap), left or right

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

At least 2 of the 4 VIIS Assessment Areas MUST have a scaling score of 3 or more. The VIIS scores will be assessed using the 5-point scale as shown in Table 10.

Any VIIS Assessment Area that is graded initially as a 3 or 4 and will be treated is followed throughout the study for this secondary endpoint. Other VIIS areas should also be graded and may also be treated at the choice of the Investigator and subject but will not be used for the analysis of this endpoint.

One of the key secondary efficacy endpoints 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 calculated using **only** the VIIS body areas described above that have a Baseline score ≥ 3.

Table 10 Visual Index for Ichthyosis Severity Score (5-Point-Scale)

Score	Category	Description
0	Clear	normal skin with no smoothening or scales
1	Almost Clear	areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
2	Mild	confluent smoothening (diminished fine skin markings; shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
3	Moderate	confluent scales (visibly separated/fractured stratum corneum) including some larger (>1cm), thick scales
4	Severe	confluent, primarily large (>1cm), thick scales

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

- On-site visual inspection of the VIIS areas
- Optional remote instead of on-site visits due to the ongoing COVID-19 pandemic comprised of both photographs and tele-medicine utilizing synchronous video conferencing technology. The severity score at each visit will be based on information gathered from both sources to yield one score and remote data cannot be used at Visits 1, 2, 6 or 9 unless there is a documented physical restriction to travel, such as COVID-19. All efforts will be made to have on-site visits, the location of all assessments will be noted in the eCRF.

8.2.3 Defining Treatment Area and Percent Body Surface

The Treatment Area includes all affected skin where the study medication will be applied (**excluding** hands, face, neck, scalp, inner thighs and genitalia) and will be determined by Investigator and subject at Visit 1 (Screening). The percent BSA that the Treatment Area comprises will be recorded at Visit 1 (Screening) and used at randomization for determining the number of kits of study medication a subject will require for the study. The calculated percent BSA of the Treatment Area will be confirmed at Visit 2 (Baseline). 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).

Note: The Treatment Area will remain the same throughout the study (unless treatment of a certain body part is discontinued due to persistent LSR).

8.2.4 Itch-Numeric Rating Scale (I-NRS)

Pruritus, from drug effect or allergic contact dermatitis, will be assessed with a self-administered electronic Patient-reported Outcome (ePRO) questionnaire using the I-NRS and WI-NRS daily through week 12. Subjects will indicate itch severity by selecting the severity level 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 7). Pruritus assessed by this evaluation should be reported as an AE only if therapy is required.

8.2.5 Dermatology Life Quality Index (DLQI)

The DLQI, is a dermatology-specific Quality of Life (QoL) instrument. Age appropriate- DLQI will be completed at the time points designated in the SoA (Table 1). The standard DLQI is a questionnaire designed for subjects aged ≥16 years that measures the impact of skin disease on the previous week's QoL. There are 10 questions related to the following topics: symptoms (from drug effect or irritant/allergic contact dermatitis), embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, treatment (see Appendix 8). Questions are scored from 0 to 30 with a possible score range from 0 (no impact of skin disease on QoL) to 30 (maximum impact on QoL). The score ranges are shown in Table 11.

Table 11 Dermatology Life Quality Index Scale

Score	Description
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 is the minimum difference in score that is meaningful for a subject. This is considered 4 points 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 QoL. There are 10 questions related to the following topics: symptoms (from drug effect or irritant/allergic contact dermatitis) and feelings, leisure, school or holidays, personal relationships, sleep, treatment (see Appendix 9). Questions are scored from 0 to 30 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 12.

Table 12 Children's Dermatology Life Quality Index Scale

Score	Description
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.

8.2.6 Ichthyosis Quality of Life (IQoL-32)

The IQoL-32 is a short and easy-to-use questionnaire containing 32 questions and organized in 7 domains (see Appendix 10). The questions are specifically dedicated to ichthyosis and explore all disease particularities such as skin pain/discomfort (from drug effect or irritant/allergic contact dermatitis), ear- and eye-related problems, heat intolerance, skin odor, scalp involvement, restrictions related to the disease (dressings, sports, leisure), expenses, psychological aspects, and consequences of the treatment: time for skin care, oily skin or clothes, and side effects. The IQoL-32 is designed for subjects >15 years of age.

8.2.7 Photography

Photographs of all four VIIS Assessment Areas (upper arms, lower legs, upper back, dorsal foot) will be taken at the time points designated in the SoA (Table 1) at preselected sites per Photographic Guide provided by the Sponsor.

8.3 Safety Assessments

8.3.1 Physical Examination

A physical examination will be performed at the time points designated in the SoA (Table 1 and Table 13), including 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 and/or Visit 9 (EOS) in the study or at Visit 8 (EOS) in the Optional Maximal Use arm will be recorded as AEs.

If there are less than two weeks between Visit 1 (Screening) and Visit 2 (Baseline), the physical examination at the Visit 2 (Baseline) includes only a dermatological assessment.

8.3.2 Vital Signs

Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured at the time points designated in the SoA (Table 1 and Table 13). Assessments will be made after the subject has rested in a seated position for at least 5 minutes in a quiet setting without distractions (e.g., television, cell phones). Height and weight will only be measured at Visit 1 (Screening).

8.3.3 Local Skin Reactions and Evaluation of Allergic Contact Dermatitis

At the time points designated in the SoA (Table 1 and Table 13, 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 the study medication.

For drug interruption due to LSRs, refer to structured drug interruption scheme (drug reduction) described in Section 7.1.

Allergic contact dermatitis is defined as a dermatitis that lasts at least 2 weeks, does not begin immediately after drug application (for example, reaction begins after first 24 hours of drug application) and becomes eczematous over time.

If at any point during treatment the Investigator believes that the subject is experiencing an allergic contact dermatitis, the subject should undergo investigator directed patch testing. as defined in Appendix 11.

8.3.4 Clinical Safety Laboratory Assessments

Urine and blood samples will be collected from each subject for safety laboratory analyses at the time points designated in the SoA (Table 1 and Table 13).

Subjects must be fasting (at least 8 hours) for Visit 1 (Screening) and, if possible, for Visit 6 and the EOS visit; however, if a subject arrives at the clinic for the EOS visit 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.

See Appendix 2 for the list of clinical laboratory tests to be performed.

8.3.5 Pregnancy Testing

Serum hCG pregnancy tests and UPT will be performed at the time points designated in the SoA (Table 1 and Table 13) for WOCBP. Women who are pregnant or breastfeeding may not be administered TMB-001 ointment.

Detailed information on pregnancy reporting is presented in Appendix 4.

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 3.

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

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.

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. The trial blind may be broken for an individual only if knowledge of the investigational medicinal product 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 EOS visit at the time points specified in the SoA (Table 1 and Table 13).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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 7.3). Further information on follow-up procedures is given in Appendix 3.

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 3.

8.4.2 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 (e.g., 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.

8.4.3 Pregnancy

An UPT will be performed at the time points designated in the SoA (Table 1 and Table 13) 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 4.

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

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 often than the protocol specified regimen of twice daily.

Oral ingestion of an 80-gram tube of TMB-001 ointment 0.05% is calculated to result in less exposure than achieved with the recommended dosage of oral isotretinoin (80 mg/day). Consequently, the theoretical occurrence of symptoms of overdosage (e.g., 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 Appendix 4 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 PK 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.

9 OPTIONAL MAXIMAL USE ARM

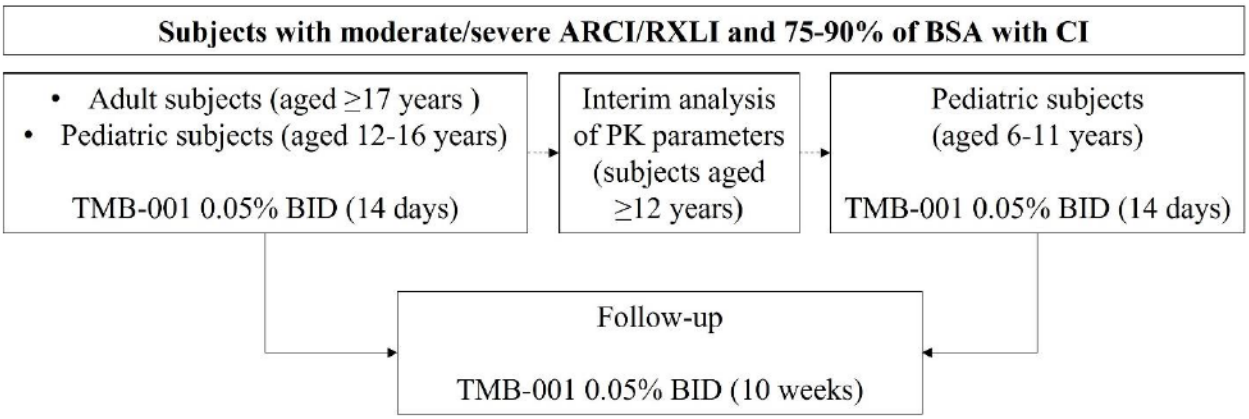
9.1 Study Design

The aim of the open-label Optional Maximal Use arm is to evaluate the systemic exposure and safety of topical TMB-001 0.05% ointment for the treatment of RXLI or ARCI under conditions of maximal use in adult and pediatric subjects.

This study arm will use a staggered entry (Figure 2):

1. Adult CI subjects (≥17 years; n=16) and pediatric CI subjects (aged 12-16 years; n=7-9) receive TMB-001 0.05% BID for 14 days.
2. Interim analysis of PK parameters for subjects aged 12 years to adult are obtained over the 15-day period.
3. Based on the exposure data of subjects aged 12 years to adult, pediatric subjects (aged 6-11 years; n=7-9) will be enrolled and receive TMB-001 0.05% BID for 14 days.
4. Following the completion of the 14-day PK period, subjects will receive an additional 10 weeks of open-label TMB-001 0.05% BID.

Figure 2 Optional Maximal Use Arm Schema



Abbreviations: ARCI = Autosomal Recessive Congenital Ichthyosis; BID = Twice Daily; BSA = Body Surface Area; CI = Congenital Ichthyosis; PK = Pharmacokinetic; RXLI = Recessive X-linked Ichthyosis

Subjects at the end of the study or subjects discontinued from the study at any time will be followed-up for additional 2 weeks for AEs.

9.1.1 Discussion of Study Design

Subjects will be enrolled according to study eligibility criteria (Sections 5.1 and 5.2). The study treatment duration for PK sampling is 14 days which is expected to be sufficient for drug accumulation to occur. Subjects will then be provided open-label TMB-001 0.05% ointment BID up to Week 12. One additional PK sample will be acquired at completion of the study to check for maintenance of steady state pharmacokinetics.

The Optional Maximal Use arm will enroll subjects with CI (instead of healthy volunteers) as there are physiological differences between diseased and healthy skin. However, the PK data from this study will be compared with oral isotretinoin (single dose of 80 mg) exposure data in healthy subjects from other studies.

Application of the TMB-001 0.05% ointment to 75%-90% of the BSA allows for a large amount of study treatment to be applied and is more in line with how TMB-001 0.05% ointment may be used in clinical practice.

The study is designed to mitigate safety risks for pediatric subjects by conducting an interim PK analysis after treatment of subjects aged 12 years to adult with BID TMB-001 0.05% ointment for 14 days. Subsequent enrollment of pediatric subjects (aged 6-11 years) will be based on exposure data of subjects aged 12 years to adult.

9.1.2 End of Study Definition

A subject is considered to have completed the study if he/she has completed the last scheduled visit (Visit 8, Table 13). The end of the study is defined as the date of the last visit of the last subject in this study.

Table 13 Schedule of Assessments Optional Maximal Use Arm

	Screening	Baseline[b]						EOS/ET	Safety follow-up
Visit[a]	**1**	**2**	**3[c] Remote possible**	**4 Remote possible**	**5[c] Remote possible**	**6[c] Remote**	**7 Remote**	**8**	**9[d] (Optional remote)**
Day	**-90 to -7**	**1**	**12**	**14**	**15**	**28 (±7 days)**	**56 (±7 days)**	**84 (±7 days)**	**98 (±2 days)**
Informed consent/assent	X								
Genetic testing/confirmation	X								
Inclusion/exclusion criteria including confirmation of % BSA	X	X[e]							
Medical history & demographics	X	X (updated)							
Physical examination[f]	X	X[g]						X	
Demonstrate how to apply the study treatment		X							
Clinical laboratory testing[h]	X							X	
Concomitant medication	X	X			X	X	X	X	
Vital signs[i]	X	X						X	
Serum hCG pregnancy test for WOCBP[j]	X								
Urine pregnancy test[k] for WOCBP[j]		X				X	X	X	
IGA-scaling and fissuring assessment		X						X	
Itch-Numeric Rating Scale		X	X	X	X	X	X	X	
Age-appropriate Dermatology Life Quality Index[l]		X						X	
Ichthyosis Quality of Life-32[m]		X						X	
Local skin reactions[n]		X	X	X	X	X	X	X	

	Screening	Baseline[b]						EOS/ET	Safety follow-up
Visit[a]	**1**	**2**	**3[c] Remote possible**	**4 Remote possible**	**5[c] Remote possible**	**6[c] Remote**	**7 Remote**	**8**	**9[d] (Optional remote)**
Day	**-90 to -7**	**1**	**12**	**14**	**15**	**28 (±7 days)**	**56 (±7 days)**	**84 (±7 days)**	**98 (±2 days)**
Subject eDiary: Train (T), Dispense (D), Review (R),		T+D	R	R	R	R	R	R	
Study treatment accountability and dispensation to subject[o]		X		X	X			X	
Pharmacokinetic assessments		X[p]	X[q]	X[r]	X[s]			X[t]	
Adverse events		X	X[u]	X	X	X	X	X[v]	X

Abbreviations: EOS = End of Study; hCG = Human Chorionic Gonadotropin; IGA = Investigator's Global Assessment

a. Visits at Screening and Baseline and EOS must be performed at the investigational site. Visits at Day 12, 14 and 15 can be performed remotely. Visits at Day 28 and Day 56 are scheduled remote visits.
b. Screening assessments (except for genetic testing) may be performed up to 90 days prior to Visit 2 (Baseline) 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 for obtaining genetic confirmation, it can be obtained at any time following consent and with no restriction until Visit 2 (Baseline).
c. Visits 3, 5 and 6 will be performed only in subjects ≥12 years.
d. Subjects at the end of the study or subjects discontinued from the study at any time will be followed-up for additional 2 weeks for AEs.
e. For subjects who require genetic testing, or a washout period related to exclusionary medications, reaffirm these subjects meet all protocol requirements at Visit 2 (Baseline).
f. Examination will include head and neck, dermatologic, cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait assessments. Additional examinations will be conducted at Visit 2 (Baseline) to identify any changes since the Screening, at Visit 8 (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.
g. If there are less than two weeks between Visit 1 (Screening) and Visit 2 (Baseline), the physical examination at the Visit 2 (Baseline) includes only a dermatological assessment.
h. Clinical laboratory tests (hematology, clinical chemistry, routine urinalysis) are provided in Table 17. Subjects must be fasting (at least 8 hours) for Visit 1 (Screening) and, if possible, at Visit 8 (EOS). However, if a subject arrives at the clinic for Visit 8 (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.
i. 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).

j. The term WOCBP is defined in Appendix 4.
k. All urine pregnancy tests must have a minimum sensitivity of 25 mIU β-hCG/mL.
l. Subjects ≥16 years will be assessed using the Dermatology Life Quality Index (DLQL) while subjects <16 years will be assessed using the Children's Dermatology Life Quality Index (CDLQI).
m. Ichthyosis Quality of Life-32 (IQoL-32) will be used for subjects >15 years.
n. For visits performed remotely, local skin reactions will be assessed via the Subject eDiary.
o. Instruction for study treatment administration will be provided in paper form and will be included in the Subject eDiary.
p. Pre-dose sample (within 1 hour before dosing) and extensive post-dose sampling (1, 2, 4, 6 and 12 hours post-dose and within 1 hour before second dose)
q. Single morning sample (pre-dose within 1 hour before morning dose)
r. Pre-dose sample (within 1 hour before morning dose) and extensive post-dose sampling (1, 2, 4, 6 and 12 hours post-dose)
s. Single morning sample (~24 hours after dose on Day 14)
t. Single sample (within ±7 days of Day 84)
u. 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/Independent Ethics Committee as an "unanticipated problem" in accordance with local procedure.
v. Any treatment-related AEs that are ongoing at Visit 8 (EOS) must be followed until resolution or stabilization.

9.2 Study Treatment

Treatments administered to subjects in the Optional Maximal Use arm, including frequencies, dosing and durations are the following:

- Study treatment will be applied to 75% to 90% of the BSA
- Subjects will be dosed for 14 days BID with TMB-001 0.05% for PK measurements. During these 14 days, any interruption of dosing, or any missed dose will result in excluding the subject from the PK sampling. It is imperative that continuous BID dosing occur days 1-14.
- Subjects will subsequently be dosed BID for an additional 70 days (10 weeks with open-label TMB-001 0.05% ointment)

9.3 Specific Assessments and Procedures

General study and safety assessments performed in the Optional Maximal Use arm are described in Section 8. The following efficacy and PK-assessments will be performed for subjects enrolled in the Optional Maximal Use arm.

9.3.1 Efficacy assessments

A limited assessment of efficacy will be conducted using the IGA (combined scaling and fissuring) scores (see Section 8.2.1) as well as the I-NRS, DLQI/CDLQI and IQoL-32 (see Sections 8.2.4 through 8.2.6) at the time points specified in the SoA (Table 13).

9.3.2 Pharmacokinetic Assessments

Blood sampling and PK analyses for subjects aged 12 years to adult will be performed at the time points designated in the SoA (Table 13) and as indicated in Table 14. PK analyses include serum levels of isotretinoin, tretinoin, 4-oxo-isotretinoin and 4-oxo-tretinoin. Blood sample collection instructions are provided in the Laboratory Manual.

Blood sampling and PK analyses for subjects aged 6 to 11 years will be performed at the time points designated in the SoA (Table 13). For these subjects, the number of blood draws will not exceed 2 time points per visit on Days 1 and 14 (total 4 blood draws, Table 15) and blood volume for PK sampling will not exceed 16 ml of blood in total (4 ml per time point). The Investigators will adhere to the site-specific blood volume limits for PK analyses to ensure minimal distress to the pediatric patients aged 6 to 11 years. Accordingly, if PK profile cannot be obtained for a given visit due to logistical challenges, the Investigator should aim to at least obtain sample for trough PK (pre-dose).

Table 14 Blood Sampling Schedule for Subjects 12 years to adult

Study Visit/Day	Sampling
Visit 2/Day 1	• Pre-dose sample, (within 1 hour before dosing)

	• Extensive post-dose sampling (1, 2, 4, 6 and 12 hours post -dose and within 1 hour before second dose)
Visit 3/Day 12	Single morning sample (pre-dose within 1 hour before morning dose)
Visit 4/Day 14	• Pre-dose sample (within 1 hour before morning dose), • Extensive post-dose sampling (1, 2, 4, 6 and 12 hours post-dose)
Visit 5/Day 15	Single morning sample (~24 hours after dose on Day 14)
Visit 8/Day 84	Single sample within ± 7 days of Day 84

Table 15 Blood Sampling Schedule for Subjects 6 to 11 years

Study Visit/Day	Sampling
Visit 2/ Day 1	Pre-dose (within one hour of dosing), single post-dose at time point to be determined
Visit 4/Day 14	Pre-dose (within one hour of dosing), single post-dose at time point to be determined

9.4 Statistical Considerations

The sample size for the Optional Maximal Use arm was requested by the FDA and no formal power calculations were performed. All analyses will be performed on the Maximal Use Population, consisting of all subjects in this study arm that received at least 1 dose of study medication.

No statistical analyses are planned, and all data collected will be provided in by-subject listings. If warranted, summary tabulations using descriptive statistics (mean, standard deviation [SD], minimum, maximum, median and % coefficient of variance) for each visit may be provided.

The safety analysis of the Optional Maximal Use arm will be performed as described in Section 10.3.1.2.

9.5 Pharmacokinetic Analysis

An interim PK analysis for the Optional Maximal Use arm of the study will evaluate the PK profile of isotretinoin and three related metabolites for 8 to 10 subjects aged ≥12 (including adults) who complete PK sampling after Day 15 of Optional Maximal Use arm dosing. At least 2 of the subjects in the interim analysis must be adolescents (aged 12 to <17 years). The evaluation will include overall bioavailability above the background of endogenous compounds:

- Tmax, defined as time to maximal plasma concentration
- Cmax, defined as maximal observed plasma concentration and
- AUCt, defined as Area under the plasma concentration-time curve from hour 0 to the last measurable plasma concentration, calculated by the linear trapezoidal method.

The results of the interim analysis will be used to determine, with highest possible accuracy, the PK sampling time points where systemic exposure for isotretinoin and the three related

metabolites is most likely in pediatric patients (aged 6 to 11 years). The first time point window will correspond to the Tmax for isotretinoin. The second time point will be used for the Tmax of isotretinoin metabolite(s) if different from isotretinoin Tmax or to estimate the elimination after Tmax for the metabolite with highest concentration above endogenous levels.

The results of the interim PK analysis will be presented in an interim report with PK profiles of analytes as measured and as change from Baseline, and derived PK parameters Cmax, Tmax, AUCt for measured and change from Baseline concentrations. The interim PK report will be reviewed by the Sponsor and will be included as a supporting document for the decisions on PK sampling windows for age group 6 to 11 years old. The memo and supporting interim PK report will be available to IRBs upon request.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Sample size calculations are based on the results of the Phase IIb study "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." Response rate assumptions for the primary endpoint (proportion of subjects achieving IGA ≥2-point improvement from Baseline) are 50% in the TMB-001 group and 10% in the vehicle group. A total sample size of 110 subjects randomized in a 2:1 ratio between TMB-001 0.05% and Vehicle will have approximately 90% power to detect a difference of 40% between the treatment groups at the 1% significance level (2-sided). The sample size also covers the proportion of approximately 15% of dropouts and non-evaluable subjects.

10.2 Populations for Analyses

For purposes of analysis, the analysis sets of the study are defined in Table 16.

Table 16 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 have a non-missing Baseline IGA assessment, received at least 50% of planned study medication, and who have no major protocol deviations that would be expected to affect efficacy measurements. 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 received at least 1 dose of study medication. Subjects will be analyzed according to the treatment they actually receive.

Abbreviations: ITT = Intent-to-treat; mITT = modified Intent-to-treat; PP = Per-protocol; SAP = Statistical Analysis Plan.

10.3 Statistical Analyses

A Statistical Analysis Plan (SAP) will be developed and finalized before database lock. The SAP 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 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, SD, minimum, and maximum will be reported for the continuous variables.

Individual subject data will be presented in listings.

10.3.1.1 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.

10.3.1.1.1 Primary Efficacy Endpoint

The difference in proportion of subjects achieving IGA treatment success at Week 12 (Visit 6) between the TMB-001 0.05% and vehicle groups will be the primary efficacy 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 improvement (decrease) in severity score as compared to Baseline. Inference will be made by comparing the proportions of treatment successes in the TMB-001 0.05% group vs the vehicle group at Week 12 using the Cochran-Mantel-Haenszel (CMH) test stratified by age (≥17, 12-16 and 6-11) and genetic subtype, a two-sided alpha of 0.01 will be used for significance testing.

The primary analysis will include a multiple imputation (MI) model that will be used to impute the measurements for subjects with missing data up to the Week 12 visit. The proportions will be calculated for 50 imputed datasets, and will be combined using Rubin's Rule to provide an overall estimate of the difference in proportions with corresponding confidence intervals and p-value (Little 2019).

Various sensitivity analyses will be performed, including (but not limited to) a tipping point analysis and a completer analysis; details will be provided in the SAP.

10.3.1.1.2 Key Secondary Efficacy Endpoints

The following key secondary efficacy endpoints will be analyzed similar to the primary efficacy endpoint at Week 12 (Periods 1 & 2):

- the difference in proportions of subjects who achieve 50% reduction from Baseline in VIIS-scaling scores in all areas with Baseline VIIS score ≥3 between TMB-001 0.05% and vehicle-treated subjects,
- the difference in proportion of subjects with IGA-scaling and fissuring scores of clear or almost clear between TMB-001 0.05% and vehicle-treated subjects,
- the difference in proportion of subjects with ≥2-point change from Baseline in IGA-scaling severity sub-scores between TMB-001 0.05% and vehicle-treated subjects, and
- the difference in proportions of subjects who achieve a ≥4-point improvement from baseline in Worst Itch-QoL scores at Week 12 in subjects with baseline Itch-Numeric Rating Scale (I-NRS) of ≥7.

It is important to ensure that reasonable certainty is achieved in the conclusions reached for key secondary endpoints. Therefore, key secondary endpoints will be adjusted for multiple statistical testing through a gatekeeping hierarchical methodology, as follows: statistical significance for the first key secondary endpoint outlined above will be declared only if the primary endpoint has previously reached statistical significance. Subsequent endpoint analyses in the order presented above will be declared significant only if the previous endpoint in order has reached statistical significance. All analyses of key secondary endpoints will be conducted at the two-sided alpha-level of 0.01. Missing data for key secondary endpoints will be handled in a similar manner as the primary endpoint.

10.3.1.1.3 Other Efficacy Endpoints

The above parameters will also be analyzed for Period 3, investigating the difference between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing at Week 24. 95% confidence intervals will be provided.

The difference in proportion of subjects with ≥2-point changes from Baseline in IGA-fissuring sub-scores at Week 12 (between TMB-001 0.05% and vehicle-treated subjects) and at Week 24 (for both scaling and fissuring scores, between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing) will be provided, along with 95% confidence intervals . CIn addition, the comparison of proportions of subjects with reduction from Baseline in DLQI or CDLQI ≥4 points at Week 12 between TMB-001 0.05% and vehicle-treated subjects will be provided, along with a 95% confidence interval. This analysis will only include adult subjects with Baseline scores of ≥11 and pediatric subjects with Baseline scores of ≥13.

Additionally, the differences in proportions of subjects with ≥4-point changes from Baseline in Worst Itch-QoL scores at Week 12 in subjects with Baseline I-NRS of ≥7 and DLQI/CDLQI (with Baseline scores of ≥11 and ≥13 for adult and pediatric subjects, respectively) between TMB-001 0.05% and vehicle-treated subjects will be provided, along with 95% confidence intervals.

The above analyses will be repeated for the maintenance phase (Period 3), comparing subjects randomized to TMB-001 0.05% BID and QD at Week 24.

10.3.1.2 Safety Analyses

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.

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.

TEAEs 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, i.e., those that occur in 5% or more of the subjects in either treatment group, will be summarized using descriptive statistics. TEAEs and relevant patient years of exposure will be presented, as appropriate.

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 clinically significant laboratory and vital signs values will also be summarized using descriptive statistics.

10.3.1.3 Other Analyses

10.3.1.3.1 Vital Signs

Descriptive statistics of vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) through Visit 9 (EOS), and change from Baseline, will be provided by treatment group

10.3.1.3.2 Physical Examinations

Findings from physical examinations (head and neck, cardiovascular, dermatological, respiratory, gastrointestinal [abdomen], and gross motor and gait assessments) will be provided at Visit 1 (Screening), Visit 6 (Week 12), and Visit 9 (EOS). Shift tables may be provided by treatment group.

10.3.1.3.3 Clinical Laboratory Tests

Clinical laboratory tests will be evaluated for any material changes during the study. All laboratory data (hematology, chemistry, and urinalysis) will be listed in the units received by the laboratory and reported using international units. Summary tables by analyte, at Visit 1 (Screening), Visit 6 (Week 12), and Visit 9 (EOS), and change from Baseline, will be presented. Shift tables may be provided by treatment group.

10.3.1.3.4 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 through Visit 9 (EOS).

10.3.1.4 Missing Data

Missing data for the primary and secondary efficacy endpoints will be handled by a multiple imputation model containing, at a minimum, Baseline values, post-baseline values, treatment, and randomization stratification factors. Imputation of missing data will be conducted under a working assumption of missing at random (MAR), meaning that the propensity for a data point to be missing is not related to the missing data, but it is related to some of the observed data.

The imputations will be performed for post-baseline visits. The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute the missing primary and secondary efficacy endpoints by treatment group. The MCMC method will impute 50 datasets in order to estimate the treatment effect, and will be combined using Rubin's Rule to provide an overall estimate of the difference in proportions with corresponding confidence intervals and p-value (Little 2019). For descriptive summary statistics, the median value across the imputed datasets will be used for subjects with missing endpoints.

Other methods for handling missing data may be explored for robustness. Full details will be provided in the SAP.

10.3.1.5 Extent of Exposure

The total amount of study medication used will be summarized using subject-reported data collected via the eDiary. Descriptive statistics (mean, median, SD, minimum, and maximum) will be determined for the total amount of study medication used by each subject by treatment group.

10.3.1.6 Dosing Compliance

Descriptive statistics will be used to summarize study treatment compliance for the ITT and PP populations. A subject will be considered compliant with the dosing regimen if the subject applies at least 50% 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.

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12 APPENDICES

Appendix 1: 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 (e.g., 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 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 6). 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 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.

Where permitted, the use of eConsent will be accessed through Datacubed's web-based application. The eConsent will include the ICF in its entirety. Consenting participants' signatures are fully FDA 21 CFR part 11 compliant. This module allows the delivery of predefined ICFs, the capture of signatures, and the delivery of comprehension questionnaires. Upon completion of the module, a PDF copy of the completed eConsent form is sent to the participant and is available for download from the site portal.

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 and the ultimate transfer of pseudonymized data to the US 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.

- Data collection and transfer using the Subject eDiary/ePRO app will be conducted in accordance with local data protection law.
- 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: 110 Allen Road, Suite 401, Basking Ridge, NJ 07920). Study administrative structure including emergency contacts, Clinical Research Organization (CRO), Laboratory, and ancillary services can be found in the Investigator Study Binder.

Medical Monitor:

[redacted]

Study Site Initiation

The Investigator must not screen any subject prior to completion of the study initiation visit, conducted by the 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 eCRFs unless transmitted to the Sponsor or designee electronically (e.g., 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.

Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IRB or IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH-GCP guidelines, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

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 (e.g., 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.

Study Conduct During the COVID-19 Pandemic

The worldwide COVID-19 pandemic may impact the conduct of clinical studies due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or study participants become potentially exposed to or infected with COVID-19. In such cases, the Sponsor will assure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity.

COVID-19 Infection in Study Subjects

There are currently no available data suggesting that patients treated with TMB-001 should have treatment interrupted during the COVID-19 pandemic. If a subject develops symptoms associated with coronavirus infection, it is recommended to confirm the diagnosis using locally approved laboratory kits and report it to the local health authorities, as required. Subjects with positive test results for SARS-CoV-2 should have this recorded as an AE, and if hospitalized, this should be reported as an SAE.

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 2: Clinical Laboratory Tests

The tests detailed in Table 17 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.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

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.

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 (e.g., SAE, AE, dose interruption), then the results must be recorded in the eCRF.

Any new or worsening of clinically significant abnormalities at the EOS visit will be recorded as AEs.

Total blood volume Main Phase 3 study

	Screening V1	V6	EOS/EOT V9	**TOTAL**	UNS
Ages 6-11 yrs	NA: 3.5mL EU: 6mL	NA: 3.5mL EU: 6mL	NA: 3.5mL EU: 6mL	NA: 10.5mL EU: 18mL	NA: 3.5mL EU: 6mL
Ages 12-17 yrs	NA: 5.5mL EU: 8mL	NA: 5.5mL EU: 8mL	NA: 5.5mL EU: 8mL	NA: 16.5mL EU: 24mL	NA: 5.5mL EU: 8mL
Ages 18+ yrs	NA: 10.5mL EU: 14mL	NA: 10.5mL EU: 14mL	NA: 10.5mL EU: 14mL	NA: 31.5mL EU: 42mL	NA: 10.5mL EU: 14mL

Total Blood Volume Maximal Use Arm

	Screening V1	V2	V3	V4	V5	EOS/EOT V8	**TOTAL**	UNS
Ages 6-11yrs	NA: 3.5mL EU: 6mL	NA: 8mL EU: 8mL	NA:0 EU:0	NA:8mL EU: 8mL	NA:0 EU:0	NA 3.5mL EU: 6mL	NA: 23mL EU: 28mL	NA:3.5mL EU: 6mL
Ages 12-17yrs	NA: 5.5mL EU: 8mL	NA: 24mL EU: 24mL	NA:4mL EU: 4mL	NA: 24mL EU: 24 mL	NA:4mL EU: 4mL	NA: 9.5mL EU: 12mL	NA: 71mL EU: 76mL	NA: 5.5mL EU: 8mL
Ages 18+yrs	NA: 10.5mL EU: 14mL	NA: 24mL EU: 24mL	NA:4mL EU: 4mL	NA: 24mL EU: 24mL	NA:4mL EU: 4mL	NA: 14.5mL EU: 18mL	NA: 81mL EU: 88mL	NA:8mL EU: 14mL

Table 17 Protocol-Required Safety Laboratory Assessments

Category	Parameters
Hematology	• Red blood cell counts (Indices: Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, % Reticulocytes) • Hemoglobin, • Hematocrit, • Platelets, • White blood cell count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)
Clinical Chemistry	• Sodium, • Potassium, • Calcium Corrected, • Magnesium, • Bicarbonate Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT), • Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT), • Alkaline Phosphatase • Total and Direct Bilirubin, • Total Protein • Fasting lipid panel (Screening, Week 12 and Week 24)
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/Serum Human Chorionic Gonadotropin (hCG) Pregnancy Test (as indicated in the SoA Table 1 and Table 13 and for Women of Childbearing Potential) • All study-required laboratory assessments will be performed by a central laboratory, with the exception of urine pregnancy testing.

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., 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, including local skin reactions. • 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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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 Advanced Clinical - Global Safety Services 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 Advanced Clinical - Global Safety Services. 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 Advanced Clinical - Global Safety Services.
- 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, e.g., 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 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 Advanced Clinical - Global Safety Services. 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 Advanced Clinical - Global Safety Services.
- 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 Advanced Clinical - Global Safety Services 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 Advanced Clinical - Global Safety Services 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/Advanced Clinical - Global Safety Services within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting via Paper CRF

- E-mail transmission of the SAE paper CRF is the preferred method to transmit this information to Advanced Clinical - Global Safety Services 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 the Investigator Study Binder. All SAEs must also be reported to Advanced Clinical - Global Safety Services within 24 hours of first awareness of the event. A paper SAE Report Form should be completed and submitted via e-mail to drugsafetypv@advancedclinical.com or faxed to 1.888.493.0910.

Appendix 4: 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 18 below.

Table 18 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.
Condoms
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.*

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 or one full menstrual cycle; whichever is longer.

Pregnancy Testing:

- WOCBP are only eligible to be included in the study after a confirmed negative serum hCG pregnancy test at Visit 1 (Screening).
- WOCBP will only be included in the study after a confirmed negative UPT at Visit 2 (Baseline). The UPT must have a minimum sensitivity of 25 mIU β-hCG.
- Additional pregnancy testing will occur at times specified in the SoA Table 1, Table 13and 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 8.4.3. 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 5: 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 isotretinoin for treatment of CI 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).
- In the samples received from subjects in the US and Canada, DNA samples will be analyzed using Congenital Ichthyosis XomeDxSlice to diagnose both RXLI and ARCI.
- If the samples are received from subjects in Europe, DNA samples will be analyzed using single gene testing for the detection of a specific panel of genes, to diagnose both RXLI and ARCI.
- 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 and are thus regulated per US regulations 42 CFR 493 and the laboratory is accredited by the College of American Pathologists.
- Causative Genes linked to ARCI:

ABCA12	ALOXE3	ALOX12B
CERS3	CYP4F22	NIPAL4
PNPLA1	SDR9C7	TGM-1

If the genetic results include any of the above mutations and the subject clinically presents with Lamellar Ichthyosis, they may be included in the study.

Appendix 6: Signature of Investigator

PROTOCOL TITLE: The ASCEND Study: A Phase III, Multicenter, Double Blinded Vehicle Controlled Study of TMB-001 - with a Parallel Optional Maximal Use Arm - in the Treatment of RXLI (X-linked) or ARCI Ichthyosis in Subjects Aged ≥6 Years

PROTOCOL NO: TMB01-301

VERSION: 2.0 25 July 2022; Protocol Amendment 1

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 7: Itch-Numeric Rating Scale

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

Contac
Email: [redacted]

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

[redacted]

Appendix 8: 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.

Appendix 9: 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 10: Ichthyosis Quality of Life (IQoL-32)

The following questions concern different periods of time. There are no right or wrong answers. Answer each one as spontaneously as possible by ticking the proposed answer that seems closest to your opinion. If a question does not concern you, tick the corresponding box.
In the past 4 weeks,

1	...has your skin been red?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
2	...has your skin been sensitive or painful (tense, uncomfortable)?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
3	...have you had dry or thick skin, with a lot of scales (dead skin)?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
4	...has your skin been itchy?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
5	...has your skin hurt because of cracking?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
6	...because of your ichthyosis, have your eyes bothered you (dryness, pain, watering, impaired vision, redness)?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
7	...because of your ichthyosis, have your ears bothered you (earwax plug, impaired hearing, pain, itching)?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
8	...did your skin have trouble adapting to temperature and/or weather changes?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
9	...have you been bothered by the smell of your skin?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
10	...have you felt like your skin was unsightly because of your disease?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
11	...does the disease make you feel dirty?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
12	...have you felt uncomfortable performing certain everyday actions (such as writing, moving) because of the pains or stiffness caused by ichthyosis?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
13	...have you felt "fatigue" in connection with your ichthyosis?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
14	...has your scalp bothered you (combing, hair care, pain, or itching)?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
	...have you performed all desired activities (sports and leisure) without fear that others might see your skin?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
15	...have you changed your vacation plans or the places you go because the planning required by your ichthyosis was too complicated?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
16	...have you felt that your ichthyosis was a handicap (aesthetic or physical), even if you do not consider yourself a handicapped person?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
17	...have you experienced mood swings because of ichthyosis?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
18	...have you felt sad, discouraged or powerless in the face of your disease?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
19	...have you felt lonely or withdrawn because of the disease?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
20	...have you experienced a feeling of anger, being "fed up", a sense of injustice because of your disease?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
21	...have you felt afraid of the future (treatments losing their effectiveness , worsening, difficulty applying the creams with age)?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
22	...have you felt afraid that the disease could restrain a romantic/sexual relationship?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
23	...have you had the unpleasant feeling of being stared at or avoided by others?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
24	...have you been afraid of being rejected or humiliated by others?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
25	...have you felt afraid that others find your skin oily, sticky or rough?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
26	...have you had bothersome side effects because of the medications?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
27	...has the disease hampered you in performing your work or going about your studies?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
28	...has your ichthyosis influenced the way you dress?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
29	...have you had a surplus of household chores because of your ichthyosis (skin flakes, oily clothes)?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
30	...have you found caring for your skin difficult and unpleasant?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
31	...has the care taken too much of your time each day?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable
32	...has the ichthyosis caused you significant expenses or inconvenient administrative procedures?	¤ tremendously	¤ a lot	¤ a little	¤ not at all	¤ not applicable

Appendix 11: Patch Testing

Contact dermatitis represents two forms of exogenous eczematous dermatitis; irritant and allergic contact dermatitis. Irritant dermatitis represents a direct toxic effect of chemicals on epidermal cells resulting in destruction of skin cells and impairment of barrier function. Allergic contact dermatitis is delayed type hypersensitivity (allergy) to small molecular weight molecules and requires initial sensitization and then subsequent elicitation. Allergic contact dermatitis most often occurs within days to weeks after repeated exposure to provocative chemicals. Allergic contact dermatitis to active ingredients and excipients of topical products is well described in the literature.

Patients suspected of having an adverse event of hypersensitivity/allergic contact dermatitis to the topically applied investigational product will be evaluated by the investigator by patch testing. If temporary withdrawal of the investigational medication does not result in amelioration of symptoms, topical corticosteroids may be employed and the patient can discontinue the trial. The presumption of possible allergic contact dermatitis will be based on the investigator's evaluation of an eczematous appearing eruption (erythematous, scaly, vesicular, or eroded patch or plaque) occurring at a previously clear site that is the recent or current recipient of the investigational product.

Patch test application sites should ideally be clinically inactive without any eczematous dermatitis, and as inactive an area of ichthyosis as is clinically practicable. The site of the patch test should not be adjacent to the currently suspected eczematous area. Patients utilizing topical corticosteroids for other local skin reactions should washout for 1 week prior to the initiation of patch testing. Flat areas such as the upper back are preferred, but alternative sites such as the ventral forearm or thigh can be used if the back is not clear. Hair bearing areas should be prepped with a safety razor to ensure adhesion of the test material.

Patch test consents and disposition of signs and symptoms will be recorded in the source document and eCRF. The investigator will apply an approximately 5 mm ribbon of investigational topical medication from the patient's existing medication supply to the interior portion of an IQ ultra patch test chamber (Chemotechnique, Sweden) and secured with additional paper tape. Two additional tests will consist of a vehicle control and white petrolatum that will be supplied by the sponsor upon request. The chambers will remain in place for approximately 48 hours (2 days). Patients will present to the clinical site for removal of the patch test and initial interpretation by the investigator. (See interpretation guideline below from the International Contact Dermatitis Research Group). Patients will return 1-4 days after removal for an additional and final interpretation of the patch test. Patch test results will be recorded in the source document and eCRF.

Patch test interpretation according to the International Contact Dermatitis Research Group (ICDRG)

?+	Doubtful
+	Mild reaction, possible erythema, infiltration and papules
+ +	Strong reaction, erythema, infiltration, papules and vesicles
+ + +	Very strong reaction, intense erythema, infiltration and coalescing vesicles
IR	Irritant reaction, of various types

Appendix 12: Abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
ARCI	Autosomal recessive congenital ichthyosis
β-hCG	Beta-human chorionic gonadotropin
BID	Twice daily
BSA	Body surface area
CDLQI	Children Dermatology Life Quality Index
CFR	Code of Federal Regulations
CI	Congenital ichthyosis
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRO	Clinical research organization
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
eCRF	Electronic case report form
eDiary	Electronic diary
EOS	End of study
ePRO	Electronic patient-reported outcome
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 Global Assessment
I-NRS	Itch-Numeric Rating Scale
IQoL-32	Ichthyosis Quality of Life -32
IRB	Institutional Review Board

ITT	Intent-to-treat
IWRS	Interactive Web Response System
LI	Lamellar ichthyosis
LSR	Local skin reactions
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mITT	Modified intent-to-treat
OTC	Over-the-counter
PP	Per-protocol
PT	Preferred term
QD	Once a day
QoL	Quality of Life
RA	Retinoic acid
ROAT	Repeat open application test
RXLI	Recessive X-linked ichthyosis
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SoA	Schedule of Assessments
SOC	System organ class
STS	Steroid sulfatase
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TGM1	Transglutaminase type 1
ULN	Upper limit of normal
UPT	Urine pregnancy test
US	United States
UV	Ultraviolet
VIIS	Visual Index for Ichthyosis Severity
VIIS-50	Visual Index for Ichthyosis Severity – Scale “treatment success”
WOCBP	Women of childbearing potential