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
NCT number: NCT05295732
Date: 04-Feb-2025

Appendix 1.9:
Documentation of Statistical Methods

Document(s) included:

Statistical Analysis Plan Addendum	21. June 2024
Statistical Analysis Plan	27. February 2024

LEO Pharma A/S

TMB01-301

Appendix date 04-Feb-2025

Statistical Analysis Plan Addendum

Protocol Number, Version and Date:
TMB01-301, Version 2.01, 14 February 2024

Statistical Analysis Plan Version and Date:
Version 3.0, 27 February 2024

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

Document Version: Final Version 1.0

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APPROVAL SIGNATURE PAGE

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

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Protocol Number: TMB01-301

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1.0 Introduction

This is an addendum to the TMB01-301 SAP Version 3.0 dated 27 February 2024. The addendum specifies additional analyses, clarifies calculation of the percent reduction in VIIS score, and specifies handling of a potential convergence issue in the multiple imputations. Unless otherwise stated, the SAP Version 3.0 still applies.

2.0 Worst Itch-QoL (WI-NRS) 4-point improvement – additional analyses

Due to an unexpectedly low number of subjects with a baseline WI-NRS score ≥7, additional analyses will be made using the threshold of a baseline WI-NRS score ≥4, ie. including in the analysis as many subjects as possible who have the possibility of obtaining a 4-point reduction. Except for the baseline threshold, the analyses will be performed as specified in the SAP Version 3.0, Section 5.2.2.3 (Week 12 analysis) and Section 5.4.3 (Week 24 analysis).

3.0 DLQI/CDLQI 4-point improvement – additional analyses

Due to an unexpectedly low number of subjects with a baseline DLQI score ≥11 (adults) or baseline CDLQI score ≥13 (pediatric subjects), additional analyses will be made using the threshold of a baseline DLQI or CDLQI score ≥4, ie. including in the analysis as many subjects as possible who have the possibility of obtaining a 4-point reduction. Except for the baseline threshold, the analyses will be performed as specified in the SAP Version 3.0, Section 5.4.2.

4.0 IGA score (combined scaling and fissuring) at Week 24 – additional analyses

In addition to the proportion of subjects with a ≥2 grade IGA improvement at Week 24, the proportion of subjects with a 1 grade improvement at Week 24 and the proportion of subjects with an IGA score of 0 or 1 at Week 24 will be tabulated. This will be done for all subjects randomized to maintenance treatment, as well as in the subgroup of subjects initially randomized to TMB-001 0.05% with a ≥2 grade IGA improvement at Week 12, the subgroup of subjects initially randomized to

TMB-001 0.05% with a 1 grade IGA improvement at Week 12 and in the subgroup of subjects initially randomized to TMB-001 0.05% with an IGA score of 0 or 1 at Week 12. The same estimand and multiple imputation approach as specified in the SAP Version 3.0, Section 5.3, for the ≥2 grade IGA improvement at Week 24 endpoint will be used. In addition, observed cases analyses will be provided. For subjects initially randomized to TMB-001 0.05%, results will be presented according to re-randomized treatment (BID or QD) using the open-label dosing presentation.

5.0 VIIS Scaling score – clarification

The percent reduction in VIIS scaling score will be calculated as the percent reduction in the average VIIS scaling score, among all treated areas with a baseline VIIS-scaling score ≥3. The calculation based on the average is equivalent with the definition of the primary endpoint in the Phase 2b trial (235-9051-202). As the ASCEND protocol did not specifically state that all areas with a baseline VIIS-scaling score ≥3 were to be treated, only areas that were identified as being treated at baseline will be included in the analyses, regardless of if treatment in those areas were discontinued at subsequent visits.

6.0 Adverse events – addition of exposure adjusted incidence rates

As requested by the FDA, all AE tables will include exposure adjusted incidence rates (EAIRs) per 100 years of exposure in addition to the number and proportion of subjects with AEs. Exposure adjusted incidence rates for a specific type of AE will be calculated as the number of subjects with the specific type of AE, divided by the total person-years at risk for the specific type of AE. For subjects with events, the time at risk is the time from the first IMP application to onset of the first event of the specific type, for subjects with no event of the specific type, the time at risk is the time from the first IMP application to the last visit.

7.0 Subgroups by ethnicity – addition

As requested by the FDA, subgroup analyses by ethnicity will be added for select efficacy and safety parameters. Since sites in the European Union (EU) did not collect ethnicity as part of demographic data, the analyses by ethnicity will have three levels: Hispanic or latino, not Hispanic or latino, and unknown.

8.0 Multiple imputation of WI-NRS scores

It is specified in the SAP Version 3.0, Section 3.9.1, that a minimum of 0 and a maximum of 10 for imputed WI-NRS values will be specified in PROC MI, in order to force PROC MI to redraw another value for imputation when an intended imputed value is outside the range from 0 to 10. In the event PROC MI cannot generate values within the specified range, the restriction may be removed in the PROC MI call and imputed values will instead be truncated (negative values will be set to 0, values over 10 will be set to 10) in an additional step following the PROC MI call. This change only applies for the WI-NRS imputation.

9.0 Efficacy figures

The following response rates, using the primary analysis methods and estimand framework, where applicable, with 95% confidence intervals will be plotted over time, with separate curves for the initial 12-week period and the 12-week maintenance period:

- IGA (combined scale and fissuring) ≥2 grade improvement
- IGA (combined scale and fissuring) score of 0 or 1
- IGA (scaling) ≥2 grade improvement
- IGA (fissuring) ≥2 grade improvement
- ≥4-point improvement in WI-NRS, among subjects with baseline WI-NRS ≥7
- ≥4-point improvement in WI-NRS, among subjects with baseline WI-NRS ≥4
- ≥50 percent reduction in the average VIIS scaling score, among all treated areas with a baseline VIIS-scaling score ≥3
- ≥25 percent reduction in the average VIIS scaling score, among all treated areas with a baseline VIIS-scaling score ≥3
- ≥4-point reduction in DLQI, among adult subjects with baseline score ≥11
- ≥4-point reduction in DLQI, among adult subjects with baseline score ≥4
- ≥4 -point reduction in CDLQI, among pediatric subjects with baseline score ≥13
- ≥4-point reduction in CDLQI, among pediatric subjects with baseline score ≥4
- ≥11-point change from baseline in IQOL-32

10.0 CHANGE HISTORY

Version	Date	Description of Changes
1.0	21 June 2024	Original Final Version

Certificate Of Completion

Envelope Id: 1A42B85C385D466F871818316176AF5D
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Initials: 0
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Statistical Analysis Plan

Protocol Number, Version and Date:
TMB01-301, Version 2.0, 25 July 2022

IND: 122058

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

Document Version: Final Version 3.0

Document Date: 27 February 2024

APPROVAL SIGNATURE PAGE

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

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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
ARCI	Autosomal Recessive Congenital Ichthyosis
ATC	Anatomic Therapeutic Class
BID	Twice Daily
BMI	Body Mass Index
BSA	Body Surface Area
CDLQI	Children Dermatology Life Quality Index
CI	Congenital Ichthyosis
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
I-NRS	Itch-Numeric Rating Scale
IQoL	Ichthyosis Quality of Life
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LSR	Local Skin Reaction
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not At Random
MSU	Mid-Study Update
MU	Maximal Use
PK	Pharmacokinetic
PP	Per Protocol
QD	Once Daily
QoL	Quality of Life
RXLI	Recessive X-linked Ichthyosis

Abbreviation	Definition
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
STS	Steroid Sulfatase
TEAE	Treatment-Emergent Adverse Event
TGM1	Transglutaminase
VIIS	Visual Index for Ichthyosis Severity
WI-NRS	Worst Itch-Numeric Rating Scale

1.0 INFORMATION FROM THE STUDY PROTOCOL

1.1 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) as well as mutations in other genes (e.g. ABCA12, ALOX12B).

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 chronic 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, particularly in the TMB-001 0.05% patient cohort.

1.2 Study Objectives

This statistical analysis plan (SAP) describes the methods to be used in the analysis of study data from clinical protocol ***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*** in order to answer the study objective(s), and is based on:

- Version 2.0 of the study protocol, dated 25 July 2022; and
- Version mid-study update (MSU) 07 of the electronic case report forms (eCRFs), dated 21 December 2023.

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this study. The SAP outlines any differences in data analysis methods relative to those planned in the study protocol. The analyses specified in this SAP supersede the analysis plan described in the study protocol and any previous versions of this SAP. Any changes to the data analysis methods after the SAP is finalized will be described in the CSR.

This SAP is not intended to cover analyses related to the primary or secondary objectives of the optional maximal use arm. It will however describe any safety reporting that answers the safety objectives.

1.2.1 Primary Objective

The primary objective of the study is to ascertain the efficacy of TMB-001 0.05% topical ointment as a treatment for CI compared with Vehicle during a 12-week treatment using the IGA score.

1.2.2 Key Secondary Efficacy Objectives

The key secondary efficacy objectives of the study are:

- To ascertain the efficacy of TMB-001 0.05% topical ointment at Week 12 using the IGA-scaling sub-scores.
- To evaluate the effect of TMB-001 0.05% topical ointment on subject Worst Itch-QoL scores at Week 12 in subjects with baseline Worst Itch-Numeric Rating Scale (WI-NRS) of ≥7.

1.2.3 Other Secondary Efficacy Objectives

Other secondary efficacy objectives of the study are:

- To ascertain the efficacy of TMB-001 0.05% topical ointment at Week 12 using the VIIS-50 scaling score.

- 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.
- To determine optimal maintenance therapy with TMB-001 0.05% topical ointment using the IGA-scaling and fissuring sub-scores.
- To determine optimal maintenance therapy with TMB-001 0.05% topical ointment using VIIS-scaling scores.

1.2.4 Patient-Reported Outcome(s) Objective

The patient-reported outcome(s) objective is 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 using the Itch-Numeric Rating scale (I-NRS/WI-NRS; collected daily during the 12-week treatment period), the Ichthyosis Quality of Life (IQoL) -32 score, and the Dermatology Life Quality Index scores (DLQI/cDLQI).

1.2.5 Safety Objectives

The safety objectives of this study are:

- To investigate the safety of topically applied TMB-001 0.05% ointment over 24 weeks.
- To evaluate incidence of suspected allergic contact dermatitis supplemented by subsequent confirmatory clinical testing.

1.2.6 Optional Maximal Use Arm Objectives

1.2.6.1 Primary Objective

The primary objective is 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.

1.2.6.2 Secondary Objective

The secondary objective is to compare systemic exposure of isotretinoin and metabolites after single or multiple applications of TMB-001 0.05% ointment cross-trial for pharmacokinetic (PK) parameters obtained for oral isotretinoin (single dose 80 mg) in healthy volunteers.

1.2.6.3 Safety Objective

The safety objective is to assess local safety and tolerability of TMB-001 0.05% ointment in adult and pediatric subjects for up to 12 weeks.

1.3 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 RXLI and 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 of RXLI or ARCI.

1.3.1 Overview of Study Design

The study consists of 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 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.

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

Optional Maximal Use Arm
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 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 additional weeks to provide additional safety and limited efficacy data.

The schedule of assessments for both the Phase 3 study and the optional maximal use arm can be found in the study protocol.

1.3.2 Randomization Methodology

For the initial randomization in Period 1, up to 110 subjects are planned to be randomized in a 2:1 ratio to receive either TMB-001 0.05% or vehicle. Randomization will be stratified by age group (6-11 years, 12-16 years, ≥17 years), and genetic subtype (RXLI, ARCI). Randomization will be performed using a permuted block design with block sizes of 3 and 6 within each stratum.

For the randomization in Period 3, all subjects initially randomized to TMB-001 0.05% are planned to be randomized in a 1:1 ratio to receive either TMB-001 0.05% BID or QD. Up to 74 subjects can be randomized, based on their responder status, defined as having a ≥1-point reduction in IGA score from Baseline at the Week 12 visit. No stratification factors are planned for this portion of the study. Randomization will be performed using a fixed block design with block sizes of 4.

Both randomizations will be performed centrally by 4G Clinical through their Interactive Response Technology (IRT).

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

Full details can be found in the Randomization Plan.

1.3.3 Sample Size Justification

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.

No formal power calculations were performed for the optional maximal use arm.

1.3.4 Participation of Independent Committees

A Data Safety Monitoring Board (DSMB) is planned for this study. There is at least one DSMB meeting planned over the course of the study. The DSMB members will be

responsible for monitoring the safety and efficacy data acquired during the study up to the time of the meeting. Full details can be found in the DSMB Charter.

1.4 Efficacy and Safety Parameters

1.4.1 Efficacy Parameters

The primary efficacy endpoint is the comparison of the proportion of subjects with ≥2-point improvement from Baseline in IGA scores (henceforth referred to as 'IGA responders') in the treatment area at Week 12 between TMB-001 0.05% and vehicle-treated subjects.

1.4.2 Key Secondary Efficacy Parameters

The key secondary efficacy endpoints include the following:

- Comparison of proportion of subjects with IGA scores of clear or almost clear at Week 12 between TMB-001 0.05% and vehicle-treated subjects.
- Comparison of proportion 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.
- Comparison of proportion of subjects with ≥4-point improvement from baseline in Worst Itch-QoL scores at Week 12 in subjects with baseline WI-NRS of ≥7 between TMB-001 0.05% and vehicle-treated subjects.

1.4.3 Other Secondary Efficacy Parameters

Other secondary efficacy endpoints include the following:

- 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.
- 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.
- 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.
- Comparison of proportions of subjects achieving ≥2-point improvement from Baseline in IGA scores at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing.
- 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.

1.4.4 Patient-reported Outcome Parameters

Patient-reported outcome endpoints include the following:

- 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.
- 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.
- 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 and WI-NRS ≥7, respectively) at Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing.
- 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.
- 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.

1.4.5 Safety Parameters

The safety endpoints include the following:

- Comparison of proportion of subjects experiencing local skin reactions (LSRs) through Week 12 between TMB-001 0.05% and vehicle-treated subjects.
- Comparison of proportion of subjects experiencing treatment-emergent adverse events (TEAEs) through Week 12 between TMB-001 0.05% and vehicle-treated subjects.
- Comparison of proportion of subjects experiencing LSRs through Week 24 between subjects randomized to TMB-001 0.05% BID and QD maintenance dosing.
- Comparison of proportion of subjects experiencing TEAEs through Week 24.
- 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.

1.4.6 Optional Maximal Use Arm Parameters

1.4.6.1 Primary Parameters

The primary endpoint is to assess individual concentrations of isotretinoin, tretinoin, 4-oxo-tretinion and 4-oxo-isotretinoin and their change from baseline.

1.4.6.2 Secondary Parameters

The secondary endpoint is to assess individual concentrations of metabolites (isotretinoin, tretinoin, and 4-oxo-isotretinoin, 4-oxo-tretinion) and their change from baseline in contemporaneously treated subjects with oral and topical isotretinoin.

1.4.6.3 Safety Parameters

The safety endpoints include the monitoring of local safety and tolerability based on dermal irritation scale, physical exam, and adverse events.

2.0 ANALYSIS POPULATIONS

2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of 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.

2.2 Per-Protocol Population

The Per-Protocol (PP) population is a 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.

2.3 Safety Population

The Safety population consists of all subjects randomly assigned to study treatment and who received at least 1 dose of study medication, including those treated in the Maximal Use Arm. Subjects will be analyzed according to the treatment they actually receive.

2.4 Maximal Use Population

The Maximum Use (MU) population is a subset of the Safety population, consisting of all subjects enrolled in the maximal use arm who receive at least 1 dose of study medication.

3.0 GENERAL ANALYSIS CONVENTION

3.1 Timing of Analyses

Analysis of topline data will be performed once all subjects complete their Week 12 (Visit 6) visit, and that all data up to that point are entered and locked within the database. Topline data minimally consists of the primary and key secondary efficacy endpoints; other disposition, demographic, safety, and efficacy parameters may be provided as well.

All remaining analyses will be performed when all subjects have either completed the study or discontinued early from the study, and all data from the study are in the clinical database, and the database is locked.

3.2 General Methods

All data listings that contain an evaluation date will contain a study day, relative to the date of first dose, designated as Day 1. Both pre-treatment and on-treatment study days are numbered related to Day 1.

All output will be incorporated into Microsoft Word or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

3.2.1 Descriptive Statistics

All data collected in the eCRFs as well as external sources will be presented in by-subject listings.

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Confidence intervals will be provided for select efficacy and safety parameters.

Assuming raw or derived variables are to 'x' decimal places, the data will be presented as follows:

- Minimum, maximum, and range to x decimal places
- Mean and median to 'x+1' decimal places
- SD to 'x+2' decimal places
- 'x+2' should be no greater than 4 decimal places

3.2.2 Hypothesis Testing

Formal statistical hypothesis testing will be performed on the primary and key secondary efficacy endpoints, with all tests conducted at the 2-sided, 0.01 level of significance. The hypothesis test for the primary efficacy analysis can be written in the form of

$$H_0\colon \hat{p}_{TMB} = \hat{p}_{VEH} \qquad \text{versus} \qquad H_1\colon \hat{p}_{TMB} \neq \hat{p}_{VEH}$$

where $\hat{p}_{TMB}$ and $\hat{p}_{VEH}$ are the proportion of IGA responders in the TMB-001 0.05% and vehicle arms, respectively. Hypothesis tests for key secondary endpoints can be written out similarly.

3.3 Computing Environment

All analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and adverse events will be coded using the Medical Dictionary for Regulator Activities (MedDRA) Version 25.0. Concomitant medications will be coded using the WHO Drug Dictionary Version March 2022.

3.4 Baseline Definitions

Unless otherwise noted, baseline is defined as the last non-missing measurement prior to the first administration of study drug. It is expected that all baseline measurements are taken on Visit 2, for all subjects.

For the DLQI, cDLQI, and IQoL-32, baseline is defined as the nominal 'Baseline' visit as reported in the PRO ediary, regardless of when this baseline record is reported.

3.5 Subgroups of Interest

Descriptive subgroup analyses may be performed by age group (6-11 years, 12-16 years, ≥17 years), and genetic subtype (RXLI, ARCI) on select safety endpoints.

Additionally, the following subgroups may be explored for both efficacy and safety parameters:

- Prior use of retinoids (Yes, No)
- Body Surface Area (BSA) Treated (≥median, <median)
- Age group (pediatric [≤17 years], adult [≥18 years])
- Remote Visits (no remote visits, ≥1 remote visit [excluding Visit 3 and Visit 8, which are per-protocol remote visits])
- Gender (male, female)
- Race (white, black or African American, Asian, other)

3.6 Methods of Pooling Data

Data from all sites will be pooled for analysis. Safety data of the optional maximal use arm may be pooled with the main study for all disposition, demographic, and safety reporting, as applicable.

3.7 Adjustments for Covariates

For all main efficacy analyses based on the Cochran-Mantel-Haenszel (CMH) approach, all stratification levels will be based on those reported in the clinical database, and not those reported through 4G Clinical's IRT system used for randomization.

3.8 Adjustments for Multiple Comparisons

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 in Section 1.4.2 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.

3.9 Missing Data Handling

3.9.1 Efficacy Data

Missing data for the primary, key secondary efficacy endpoints, and select other secondary endpoints will be handled by a multiple imputation model containing baseline values, post-baseline values collected at an in-person visit (i.e. not collected remotely), treatment (TMB-001 0.05% or Vehicle for the Week 12 endpoints, TMB-001 0.05% BID or QD for the Week 24 endpoints), 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 following steps will be taken:

1) For all scores, the missingness pattern in the data will be evaluated. If the pattern is not monotone, the MCMC method of SAS PROC MI will be used to make it monotone. The minimum values for imputed variables will be set to 0, in order to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. For IGA scores (including scaling and fissuring sub-scores) and the VIIS scores, the maximum value for imputed variables will be set to 4, in order to force PROC MI to redraw another value for imputation when an intended imputed value is greater than the 4. For the I-

NRS/WI-NRS, the maximum value for imputed variables will be set to 10. Imputed values will be rounded to the nearest integer.

2) SAS PROC MI will be used for imputing missing values of data with monotone missing pattern. If the MCMC method of step 1 was previously employed, one imputation will be made using each of the 50 MCMC-imputed datasets. If the MCMC method of step 1 was not previously employed, 50 imputations will be created assuming the data are missing at random (MAR).
3) A linear regression model will be used to impute all scores individually, using the treatment arm and non-missing scores from earlier scheduled timepoints. All response statuses will be calculated from the imputed scores.

The resulting analysis of the multiply imputed data will be outlined in Section 5.

3.9.2 Adverse Event Data

When tabulating AE data, partial start dates will be handled as follows:

- If the year, month, and day are all missing, then set the onset day to the date of the first dose.
- If the month and day are missing, and the year is:
    - the same as the year of first dose, then set the onset day as the date of the first dose;
    - earlier than the year of first dose, then set the onset day as December 31;
    - after the year of the first dose, then set the onset day as January 1.
- If only the day is missing, then
    - if the month/year is the same as the first dose, then set the onset day as the date of first dose;
    - if the month/year is earlier than the month/year of the first dose, then set the onset day as the last day of the month;
    - if the month/year is later than the month/year of the first dose, then set the onset day as the first day of the month.

Partial end dates will only be imputed if the year is non-missing:

- If the month and day are missing, and the year is the same as the year of the last dose then set the end day as the last day of the month of the first dose. Otherwise, set the end date as December 31.
- If only the day is missing, then set the end day as the last day of the month.

If the imputed start date is later than the imputed end date then set the imputed start date to the imputed end date.

3.9.3 Prior and Concomitant Medication Data

When tabulating prior/concomitant medication data, partial start dates will be handled as follows:

- If the year, month, and day are all missing, then set the start date to the date of first dose.
- If the month and day are missing and the year is earlier than the year of the first dose, then set the start date to December 31. Otherwise, set the start date to the date of first dose.
- If only the day is missing, if the month/year is earlier than the month/year of the first dose then set the start date to the first day of the month. Otherwise, set the start date to the last day of the month.

Partial end dates will only be imputed if the year is non-missing:

- If the month and day are missing then set the end date to December 31.
- If only the day is missing, then set the end day as the last day of the month.

If the imputed start date is later than the imputed end date then set the imputed start date to the imputed end date.

3.10 Visit Windows

It is expected that all visits should occur according to the protocol schedule within the allowed protocol-specified window. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the protocol-specified visit window. For the Week 12 visit (Visit 6), an analysis window will be created with a larger interval to allow in-person unscheduled visits within the interval to act as the nominal Week 12 visit; the analysis window will consist of the target day, plus or minus 14 days. For any other visit, ff an unscheduled visit occurs within the allowed protocol-specified window and there are no scheduled visits reported, the unscheduled visit may act as the planned visit. If there are multiple visits in a same visit window, the median value will be used for analysis.

3.11 Data Presentation

3.11.1 Disposition, Demographics, and Baseline Characteristics

Disposition, demographics, and baseline characteristics data for all subjects (including those enrolled in the optional maximal use arm) will be pooled for analysis.

TMB-001 0.05% (N=xx)	Vehicle (N=xx)	Phase 3 Overall (N=xx)	Maximal Use Arm (N=xx)	Overall (N=xx)

This data presentation will be used for all analyses described in Section 4 below.

3.11.2 Efficacy

Efficacy data for all subjects will have two presentations, depending on the endpoints being analyzed. For the primary, key secondary, and select other secondary efficacy endpoints, the data presentation (henceforth referred to as 'primary efficacy data presentation') will have the following header:

TMB-001 0.05% (N=xx)	Vehicle (N=xx)

For endpoints analyzed on parameters collected during Period 3, a secondary data presentation will be used (henceforth referred to as 'open-label dosing efficacy data presentation), with the following header:

	OL TMB-001 0.05% BID (N=xx)		
OL TMB-001 0.05% QD (N=xx)	TMB-001 0.05% in Blinded Phase (N=xx)	Vehicle in Blinded Phase (N=xx)	Total OL TMB-001 0.05% BID (N=xx)

An overall column is not planned for any efficacy output, however it may be added, if warranted.

3.11.3 Safety

The primary data presentation for all safety analyses (henceforth referred to as 'primary safety data presentation') will have the following table header:

TMB-001 0.05% (N=xx)	Vehicle (N=xx)	Overall (N=xx)

The TMB-001 0.05% and Vehicle columns will represent the subjects initially randomized to either TMB-001 0.05% or vehicle, regardless of the second randomization allocation in Period 3.

Additionally, a data presentation specific to Period 3 will be used:

	OL TMB-001 0.05% BID (N=xx)			
OL TMB-001 0.05% QD (N=xx)	TMB-001 0.05% in	Vehicle in Blinded	Total OL TMB-001 0.05% BID (N=xx)	Overall (N=xx)

	Blinded Phase (N=xx)	Phase (N=xx)		

This data presentation (henceforth referred to as 'open-label dosing safety data presentation') will be used for all analyses of safety endpoints specifically during Period 3, comparing TMB-001 0.05% BID and QD maintenance dosing.

3.12 Interim Analysis

There is no interim analysis planned for this study.

4.0 DISPOSITION, PROTOCOL DEVIATIONS, DEMOGRAPHICS AND BASELINE ANALYSES

All analyses in this section will be performed using the Safety Population and presented using the data presentation described in Section 3.11.1, unless otherwise indicated.

4.1 Disposition

Subject disposition will be tabulated by treatment group and overall, based on all subjects screened. The number of subjects and percentages will be provided for the number screened, the number randomized, the number treated, the number re-randomized in Period 3, the number in each analysis population, the number who completed each period, the number who completed the study, the number who withdrew prior to completion and the reason(s) for withdrawal.

A by-subject data listing of disposition data will be provided, including a separate data listing for inclusion/exclusion information.

4.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be tabulated and will be summarized using descriptive statistics. Variables include: age (years), sex, race, ethnicity, height, weight, and BMI. All variables will be reported as collected in the eCRFs except for BMI, which will be computed using height and weight such that BMI = weight (kg) / [height (m)]^2. Demographic and baseline data for each subject will be provided in data listings.

Demographics and baseline characteristics summaries will be provided for the ITT and PP Populations in addition to the Safety Population.

Medical history will be coded using MedDRA v25.0 and presented by system organ class and preferred term. If a subject had more than one medical history event within a system organ class, the subject is counted once for each preferred term and once for the system organ class. The table will be sorted by descending frequency, based on the overall column of the data presentation. Medical history data will also be provided in a by-subject listing.

A by-subject listing of pregnancy test results will be provided.

4.3 Baseline Disease Characteristics

The type of CI (both as reported in the IRT and in the EDC) and specific mutation will be tabulated, in addition to whether the test was performed prior to or as part of the screening portion of the study. The time since initial clinical diagnosis of CI, as well as

the total percent body surface area (BSA) affected with CI will be summarized using descriptive statistics.

Prior medications specific for the treatment of CI will be tabulated, such as the use of over-the-counter products and emollients, oral retinoids, UV light, systemic corticosteroids, and topical retinoids.

All baseline disease characteristics will be provided in by-subject data listings.

4.4 Protocol Deviations

All protocol deviations that could compromise the interpretation of efficacy or safety of the study drug will be considered as major deviations. The Sponsor will be responsible for approving the final protocol deviation; this file will include a description of the protocol deviations and clearly identify whether this deviation warrants exclusion from the PP Population. This file will be finalized prior to database lock/unblinding for the execution of the primary analysis.

A summary tabulation of major protocol deviations will be provided. All protocol deviations will be presented in a by-subject data listing.

4.4.1 Deviations Related to COVID-19

Protocol deviations due to COVID-19 will be reported in a separate by-subject data listing. All visits and assessments impacted by COVID-19 will be listed.

5.0 EFFICACY ANALYSIS

5.1 Primary Efficacy

All analyses in this section will be presented as described in Section 3.11.2, unless otherwise indicated.

All source data for all efficacy parameters will be provided in by-subject data listings.

All efficacy measurements over time will also be tabulated using descriptive statistics, as well as presented graphically using by-subject line plots, where only those subjects who are eligible to be responders will be provided.

5.1.1 Estimand

The primary estimand is defined by the following:

- Population: Subjects in the ITT population as defined by protocol eligibility criteria.
- Variable: the proportion of subjects with a ≥2-point improvement in the IGA score at Week 12 compared to baseline.
- The following intercurrent events and their handling include:
    - Treatment discontinuation prior to Week 12 due to adverse event or lack of efficacy: Composite variable strategy, where the discontinuation may be considered informative about the subject's outcome and will therefore consider these subjects as non-responders.
    - Modification to dose level: Treatment policy strategy, where results will be used regardless of dose modifications.
    - Use of prohibited medication: Composite variable strategy, where the use of such medication may be considered informative about the subject's outcome (e.g., subjects are using prohibited medications due to perceived lack of efficacy of study drug) and will therefore consider these subjects as non-responders.
- Population-level summary: The difference in proportions of subjects achieving IGA response at Week 12 between treatment groups (TMB-001 0.05% and vehicle).

5.1.2 Primary Analysis Methods

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 "responder" (treatment success) or "non-responder" (treatment failure), where a responder is defined as at least a 2-grade improvement (decrease) in severity in the IGA 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 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, along with 99% and 95% confidence intervals.

Missing Week 12 data will be imputed, as outlined in Section 3.9.1, and IGA responder status will be derived from the imputed values. A CMH analysis will be performed on each of the 50 imputed datasets. The results from the CMH analyses will be combined using the Wilson-Hilferty transformation by Ratitch et al. (Ratitch et al. 2013) to produce a pooled CMH statistic and p-value. The differences in proportions and standard errors will be combined using Rubin's Rule (Little 2019) the SAS PROC MIANALYZE. The pooled Mantel-Haenszel stratum-weighted estimator of the difference in proportion and the associated standard error will be used to produce the 99% confidence interval based on the large-sample approximation method for binary data without using continuity correction. The 95% confidence interval will also be provided.

A summary of the occurrences of intercurrent events of each type will be provided by treatment group.

5.1.3 Sensitivity Analysis Methods

The following sensitivity analyses are planned to show the robustness of the primary analysis:

1) The primary analysis will be repeated using the PP population (using the same CMH test and the same MCMC multiple imputation method).
2) The primary analysis will be repeated using the set of subjects with non-missing Week 12 IGA assessment using both the ITT and PP populations (i.e., a completer's analysis).
3) The primary analysis will be repeated on both the ITT and PP populations by imputing missing Week 12 data using last observation carried forward (LOCF).
4) A tipping point analysis will be performed using the observed data to assess the potential impact of missing Week 12 IGA scores on the primary analysis result. The following steps will be followed to implement the tipping point analysis:
    a. Determine the number of missing IGA scores at Week 12 in the TMB-001 0.05% treatment group (n_{1m}) and Vehicle group (n_{2m}) in the ITT population
    b. Let s_1 represent the number of IGA responders in missing TMB-001 0.05% group. Let s_2 represent the number of IGA responders in the Vehicle group
    c. Set both $s_1 = 0$ and $s_2 = 0$
    d. From 0 to $n_{1m,}$ calculate the difference in proportions and corresponding p-value of the difference between the treatment groups, where each iteration is $s_1 = s_1 + 1$, using a CMH test

e. From 0 to $n_{2m,}$ calculate the difference in proportions and corresponding p-value of the difference between the treatment groups, where each iteration is $s_2 = s_2 + 1$, using a CMH test
f. Present the p-value from each analysis combination of s_1 and s_2 in steps (d) and (e) in a matrix (e.g. a heatmap)
g. Determine the "tipping point" of the results where the difference in proportions is significant at the 0.01 level

5) The primary analysis will be repeated on the ITT population by imputing missing Week 12 IGA scores on the basis of a pattern-mixture model under the missing not at random (MNAR) assumption. Specifically, a control-based pattern imputation will be performed, as described by Ratitch and O'Kelly (Ratitch and O'Kelly 2011).
6) Treatment effect will be analyzed via generalized estimating equations (GEEs) using SAS PROC GENMOD, with IGA response as the dependent variable, and treatment group, age group, CI type, visit, and treatment by visit interaction as independent variables. Week 12 odds ratios and 95% confidence intervals will be provided.
7) If there are discrepancies between the CI subtypes reported in the IRT and those reported in the EDC, the primary analysis will be repeated using the CI subtypes reported in the IRT rather than those reported in the EDC.

5.2 Key Secondary Efficacy Analysis

All analyses in this section will be presented as described in Section 3.11.2, unless otherwise indicated. All analyses will be primarily performed using the ITT population, unless otherwise noted.

5.2.1 Estimands

The estimands of the key secondary endpoints can be written out in a similar manner as the estimand of the primary endpoint. High-level descriptions of estimands are outlined in the following table:

Table 1. Attributes of Estimands for Key Secondary Endpoints

	Endpoint		
	Difference in proportions of subjects with IGA-scores of clear/almost clear	Difference in proportions of subjects with ≥2-point change IGA-scaling severity sub-scores	Difference in proportions of subjects with ≥4-point improvement in worst Itch-QoL

Population	Subjects in the ITT population as defined by protocol eligibility criteria	Subjects in the ITT population as defined by protocol eligibility criteria	Subjects in the ITT population as defined by protocol eligibility criteria with baseline WI-NRS of ≥7
Variable	Proportion of IGA clear/almost clear score responders	Proportion of IGA-scaling sub-score responders	Proportion of worst Itch-QoL responders
Intercurrent Events and Strategies	1) Composite variable strategy for treatment discontinuations due to adverse event or lack of efficacy 2) Treatment policy strategy for dose modifications 3) Composite variable strategy for use of prohibited medications		
Population-level Summary	The difference in proportions of subjects achieving responses at Week 12 between the TMB-001 0.05% and vehicle treatment groups		

5.2.2 Analysis Methods

Statistical testing will be performed on the key secondary efficacy endpoints using a two-side alpha of 0.01, according to the following hierarchical order.

5.2.2.1 IGA Clear Score Responders at Week 12

The difference in proportions of subjects with IGA score of clear or almost clear (henceforth referred to as 'IGA clear score responders') versus mild/moderate/severe will be computed at Week 12, between the TMB-001 0.05% and vehicle treatment groups.

The difference in proportions will be calculated in a similar manner as the primary efficacy endpoint using the CMH test, including the use of 50 multiply imputed datasets combined using the Wilson-Hilferty transformation for the pooled CMH statistic and Mantel-Haenszel stratum-weighted difference in proportions combined using Rubin's rule. Results will be provided using the primary efficacy data presentation.

5.2.2.2 IGA-Scaling Sub-Score Responders at Week 12

The difference in proportions of subjects with a ≥2 point change from baseline in IGA-scaling severity sub-scores (henceforth referred to as 'IGA-scaling sub-score responders') will be computed at Week 12 among subjects who have a score of ≥3 at baseline, between the TMB-001 0.05% and vehicle treatment groups.

The difference in proportions will be calculated in a similar manner as the primary efficacy endpoint using the CMH test, including the use of 50 multiply imputed datasets combined using the Wilson-Hilferty transformation for the pooled CMH statistic and Mantel-Haenszel stratum-weighted difference in proportions combined using Rubin's rule. Results will be provided using the primary efficacy data presentation.

5.2.2.3 Worst Itch-QoL (WI-NRS) Responders at Week 12

The difference in proportions of subjects achieving a ≥4-point improvement from baseline in weekly Worst Itch-QoL scores on the WI-NRS (henceforth referred to as 'Worst Itch-QoL (WI-NRS) responders') will be computed at Week 12, between the TMB-001 0.05% and vehicle treatment groups. Only subjects with baseline WI-NRS scores of ≥7 will be included in this analysis.

The WI-NRS scores will be collected daily, where the weekly average scores will be mapped to each protocol-specified visit and used for analysis, as appropriate. The daily scores to be used will depend on actual visit dates; daily scores of the 6 days prior to the Week 12 visit will be averaged with the daily score reported on the Week 12 visit date to create the weekly average for the Week 12 visit. A weekly average can only be computed if there are ≥4 daily scores reported, otherwise the weekly score will be considered missing. Early subjects do not have daily scores collected prior to baseline (in order to derive baseline weekly averages). In such cases, the single baseline score will be used for analysis.

The difference in proportions will be calculated in a similar manner as the primary efficacy endpoint using the CMH test, including the use of 50 multiply imputed datasets combined using the Wilson-Hilferty transformation for the pooled CMH statistic and Mantel-Haenszel stratum-weighted difference in proportions combined using Rubin's rule. Results will be provided using the primary efficacy data presentation.

For completeness, a descriptive analysis of the I-NRS will also be provided, as applicable.

5.2.3 Sensitivity Analysis Methods

Sensitivity analyses of all key secondary endpoints will include:

1) Repeat analyses using the PP population (using the same CMH test and the same MCMC multiple imputation method).
2) Repeat analyses using the set of subjects with non-missing Week 12 data using both the ITT and PP populations (i.e., a completer's analysis).
3) If there are discrepancies between the CI subtypes reported in the IRT and those reported in the EDC, the key secondary analyses will be repeated using the CI subtypes reported in the IRT rather than those reported in the EDC.

5.3 Other Secondary Efficacy Analysis

5.3.1 Estimands

The estimands of the other secondary endpoints can be written out in a similar manner as the estimands of the key secondary endpoints. High-level descriptions of estimands are outlined in the following table:

Table 2. Attributes of Estimands for Other Secondary Endpoints

	Endpoint				
	Difference in proportions of subjects with VIIS-scaling score reduction of 50%	Difference in proportions of subjects with VIIS-scaling score reduction of 25%	Difference in proportions of subjects with ≥2-point improvement in IGA fissuring sub-scores	Difference in proportion of subjects with ≥2-point improvement in IGA score, IGA scaling and fissuring sub-scores	Difference in proportions of subjects with VIIS-scaling score reduction of 50%
Population	Subjects in the ITT population as defined by protocol eligibility criteria	Subjects in the ITT population as defined by protocol eligibility criteria	Subjects in the ITT population as defined by protocol eligibility criteria with baseline fissuring sub—score of ≥3	Subjects in the ITT population as defined by protocol eligibility criteria with baseline scaling/ fissuring sub—score of ≥3	Subjects in the ITT population as defined by protocol eligibility criteria
Variable	Proportion of VIIS 50% reduction responders among areas with baseline VIIS score ≥3	Proportion of VIIS 25% reduction responders among areas with baseline VIIS score ≥3	Proportion of worst IGA fissuring sub-score responders	Proportion of IGA responders, /IGA scaling sub-score responders, IGA fissuring sub-score responders	Proportion of VIIS 50% reduction responders among areas with baseline VIIS score ≥3
Intercurrent Events and Strategies	1) Composite variable strategy for treatment discontinuations due to adverse event or lack of efficacy 2) Treatment policy strategy for dose modifications 3) Composite variable strategy for use of prohibited medications				
Population-level Summary	The difference in proportions of subjects achieving responses at Week 12 between the TMB-001 0.05% and vehicle treatment groups			The difference in proportions of subjects achieving responses at Week 24 between the TMB-001 0.05% BID and QD dosing groups	

5.3.2 Analysis Methods

All analyses in this section will be presented as described in Section 3.11.2, unless otherwise indicated. All analyses will be primarily performed using the ITT population, unless otherwise noted. No formal inference is intended to be performed on other secondary efficacy endpoints, however 95% confidence intervals will be provided. The estimand framework will be applied for all analyses using multiple imputation.

5.3.2.1 VIIS-Scaling Score 50% Reduction Responders at Week 12

The difference in proportions of subjects achieving at least a 50% reduction on average from baseline in VIIS-scaling score in all areas with baseline VIIS score ≥3 will be computed at Week 12 along with 95% confidence intervals, between the TMB-001 0.05% and vehicle treatment groups. The difference in proportions will be calculated in a similar manner as the primary efficacy endpoint using the CMH test, including the use of 50 multiply imputed datasets combined using the Wilson-Hilferty transformation for the pooled CMH statistic and Mantel-Haenszel stratum-weighted difference in proportions combined using Rubin's rule. Only the areas with baseline VIIS scores of ≥3 will be included in this analysis. Areas may include the upper back, the upper arm, the shin/lower leg, and the dorsal foot. Individual areas may reach a 50% reduction; however, subjects will be considered responders only if the average of all areas with baseline VIIS scores of ≥3 achieve a 50% reduction.

The analysis will be repeated using observed data only. The Mantel-Haenszel stratum-weighted estimator of the difference in proportion and the associated standard error will be used to produce a 95% confidence interval.

Results will be provided using the primary efficacy data presentation.

This analysis will be repeated using the PP population.

5.3.2.2 VIIS-Scaling Score 25% Reduction Responders at Week 12

The difference in proportions of subjects achieving at least a 25% reduction on average from baseline in VIIS-scaling score in all areas with baseline VIIS score ≥3 at Week 12 between TMB-001 0.05% and vehicle treatment groups will be computed in a similar manner as the primary efficacy endpoint using the CMH test, including the use of 50 multiply imputed datasets combined using the Wilson-Hilferty transformation for the pooled CMH statistic and Mantel-Haenszel stratum-weighted difference in proportions combined using Rubin's rule., along with 95% confidence intervals. Individual areas may reach a 25% reduction; however, subjects will be considered responders only if the average of all areas with baseline VIIS scores of ≥3 achieve a 25% reduction.

The analysis will be repeated using observed data only. The Mantel-Haenszel stratum-weighted estimator of the difference in proportion and the associated standard error will be used to produce a 95% confidence interval.

Results will be provided using the primary efficacy data presentation.

5.3.2.3 IGA-Fissuring Sub-Score Responders at Week 12

The difference in proportions of subjects with a ≥2 point change from baseline in IGA-fissuring severity sub-scores will be computed at Week 12 among subjects who have a score of ≥3 at baseline, between the TMB-001 0.05% and vehicle treatment groups will be computed in a similar manner as the primary efficacy endpoint using the CMH test, including the use of 50 multiply imputed datasets combined using the Wilson-Hilferty transformation for the pooled CMH statistic and Mantel-Haenszel stratum-weighted difference in proportions combined using Rubin's rule., along with 95% confidence intervals.
The analysis will be repeated using observed data only. The Mantel-Haenszel stratum-weighted estimator of the difference in proportion and the associated standard error will be used to produce a 95% confidence interval.

Results will be provided using the primary efficacy data presentation.

This analysis will be repeated using the PP population.

5.3.2.4 IGA Score, IGA Scaling Sub-Score, and IGA Fissuring Sub-score Responders at Week 24

The difference in proportions of subjects achieving a ≥2 grade improvement from baseline in the IGA score, the IGA Scaling sub-score, and IGA fissuring sub-score will each be computed at Week 24, between the TMB-001 0.05% BID and QD maintenance dosing groups will be computed in a similar manner as the primary efficacy endpoint using the CMH test, including the use of 50 multiply imputed datasets combined using the Wilson-Hilferty transformation for the pooled CMH statistic and Mantel-Haenszel stratum-weighted difference in proportions combined using Rubin's rule., along with 95% confidence intervals.
The analyses will be repeated using observed data only. The Mantel-Haenszel stratum-weighted estimator of the difference in proportion and the associated standard error will be used to produce a 95% confidence interval.

Results will be provided using the open-label dosing efficacy data presentation.

These analyses will be repeated using the PP population.

5.3.2.5 VIIS-Scaling Score 50% Reduction Responders at Week 24

The difference in proportions of subjects achieving at least a 50% reduction on average from baseline in VIIS-scaling score in all areas with baseline VIIS score ≥3 at Week 24 between TMB-001 0.05% BID and QD maintenance dosing groups will be computed in a similar manner as the primary efficacy endpoint using the CMH test, including the use of 50 multiply imputed datasets combined using the Wilson-Hilferty transformation for the pooled CMH statistic and Mantel-Haenszel stratum-weighted difference in proportions combined using Rubin's rule., along with 95% confidence intervals. Individual areas may reach a 50% reduction; however, subjects will be considered responders only if the average of all areas with baseline VIIS scores of ≥3 achieve a 50% reduction.
The analysis will be repeated using observed data only. The Mantel-Haenszel stratum-weighted estimator of the difference in proportion and the associated standard error will be used to produce a 95% confidence interval.

Results will be provided using the open-label dosing efficacy data presentation.

5.4 Patient-Reported Outcomes Analysis

All analyses in this section will be presented as described in Section 3.11.2, unless otherwise indicated. All analyses will be primarily performed using the ITT population, unless otherwise noted. No formal inference is intended to be performed on patient-reported outcomes.

5.4.1 IQoL-32 Responders at Week 12 and Week 24

The IQoL-32 contains 32 items, each scored from 0 to 4 ('not applicable', 'not at all', 'a little', 'a lot', 'tremendously') for a total score that varies between 0 and 128. The difference in proportions of subjects achieving an ≥11-point change from baseline in IQoL-32 scores will be compared at Week 12 (between TMB-001 0.05% and vehicle treatment groups) and at Week 24 (between TMB-001 0.05% BID and QD maintenance dosing groups) computed based on the CMH method (stratified by CI type), along with 95% Wald confidence intervals. No imputation will be performed for missing Week 12 or Week 24 data. Results will be provided using the primary efficacy data presentation for the Week 12 analysis, and open-label dosing efficacy data presentation for the Week 24 analysis. Only subjects that are ≥16 years of age will be included in these analyses.

The Week 12 analysis will be repeated using the PP population. Additionally, the difference in proportions at Week 24 will be compared against Week 12, where 95% Wald confidence internals will be provided.

Sensitivity analyses will be performed for both Week 12 and Week 24 analyses, where questions pertaining to areas of the body where TMB-001 is explicitly not administered (e.g., eyes, ears, and scalp) will be omitted. Questions 6, 7 and 14 of the IQoL-32 will

be removed from the analysis, and the total score for this sensitivity analysis will vary between 0 and 116.

5.4.2 DLQI/CDLQI Responders at Week 12 and Week 24

The difference in proportions of subjects achieving an ≥4-point change from baseline in DLQI/CDLQI scores will be compared separately for adult and pediatric subjects at Week 12 (between TMB-001 0.05% and vehicle treatment groups) and at Week 24 (between TMB-001 0.05% BID and QD maintenance dosing groups) computed based on the CMH method (stratified by CI type), along with 95% Wald confidence intervals. Adult subjects will be compared using the DLQI scores among adults with baseline scores of ≥11, and pediatric patients will be compared using the CDLQI scores among pediatric subjects with baseline scores of ≥13. No imputation will be performed for missing Week 12 or Week 24 data. Results will be provided using the primary efficacy data presentation for the Week 12 analysis, and open-label dosing efficacy data presentation for the Week 24 analysis.

Additionally, the difference in proportions at Week 24 will be compared against Week 12, where 95% Wald confidence intervals will be provided.

5.4.3 WI-NRS Responders at Week 24

The difference in proportions of subjects achieving a ≥4-point improvement from baseline in weekly Worst Itch-QoL scores on the WI-NRS will be compared at Week 24, between the TMB-001 0.05% BID and QD maintenance dosing groups, computed in a similar manner as the primary efficacy endpoint using the CMH test, including the use of 50 multiply imputed datasets combined using the Wilson-Hilferty transformation for the pooled CMH statistic and Mantel-Haenszel stratum-weighted difference in proportions combined using Rubin's rule., along with 95% confidence intervals. Only subjects with baseline WI-NRS scores of ≥7 will be included in this analysis.

Unlike what is described in section 5.2.2.4, daily scores are not computed post-Week 12 visit, and so the difference in proportion at Week 24 will be computed using the results collected on Week 24, compared to baseline. In addition, the difference in proportions at Week 24 will be compared against Week 12, where 95% confidence intervals will be provided. Both analyses will be performed using multiply imputed data.

The analysis will be repeated using observed data only. The Mantel-Haenszel stratum-weighted estimator of the difference in proportion and the associated standard error will be used to produce a 95% confidence interval.

Results will be provided using the open-label dosing efficacy data presentation.

For completeness, a descriptive analysis of the I-NRS will also be provided, as applicable.

5.5 Efficacy in the Maximal Use Arm

All efficacy data collected from subjects in the maximal use arm will be listed in by-subject data listings. No formal comparison will be made with the results of the main Phase 3 study.

6.0 PHARMACOKINETICS/PHARMACODYNAMICS ANALYSIS

Pharmacokinetic and pharmacodynamic analyses are outside of the scope of this SAP. Details will be provided in a separate PK data analysis plan.

7.0 SAFETY ANALYSIS

All analyses in this section will be performed using the Safety Population and presented as described in Section 3.11.3, unless otherwise indicated.

7.1 Study Drug Exposure and Compliance

All study drug exposure and compliance analyses will be performed on primary dosing (Periods 1 & 2) alone, open-label dosing (Period 3) alone, and all periods combined, unless otherwise noted.

For all parameters below, the following rules apply:

- Primary dosing is considered as the time where study drug was applied to complete requirements of Periods 1 & 2
    - The date of first dose of primary dosing is the date where the first dose was administered in Period 1
    - The date last dose of primary dosing is the date where the last dose was administered in Period 2
- Open-label dosing is considered as the time where study drug was applied to complete requirements of Period 3
    - The date of first dose of open-label dosing is the date where the first dose was administered in Period 3
    - The date of last dose of open-label dosing is the date where the last dose was administered in Period 3
- Combined dosing consists of both primary and open-label dosing.
    - The date of first dose of combined dosing is the date where the first dose was administered in Period 1
    - The date of last dose of combined dosing is the date where the last dose was administered in Period 3

Overall duration of study drug exposure will be calculated as the number of days subjects were administered study drug, as below, and will be summarized using descriptive statistics.

$$Duration\ (days) = (date\ of\ last\ dose - date\ of\ first\ dose) + 1$$

Duration of treatment, defined as the number of days dosed, will also be provided for comparison.

Dosing compliance will be summarized using descriptive statistics, and is defined as

$$Dosing\ Compliance\ (\%) = \frac{Number\ of\ Actual\ Doses\ Applied}{Number\ of\ Expected\ Doses\ Applied}$$

The number of expected doses applied will be dictated by a subject's status on the study. Specifically, doses that would be expected will not contribute to the denominator if they occur after a subject has discontinued from the study.

The number of subjects and percentages of subjects with <50% versus ≥50%, and <80% versus ≥80% dosing compliance will be presented. For subjects with missing doses, the number and percentages will be provided, along with the reasons why the doses were missed.

The total amount of study drug applied (in grams) will be summarized using descriptive statistics based on the data provided by the weighing of study drug tubes. A full – unused – tube's weight averages 101g. Any returned tube weighing more than 101g will be set to 101g. The assumption that the amount of study drug that was removed from the tube is equivalent to the amount of study drug applied will be used.

Additionally, actual dose intensity (g/day), defined as the ratio of total drug applied and the duration of study drug exposure will be summarized using descriptive statistics.

Data collected in the eDiary will be summarized using descriptive statistics, as applicable.

Specifically for Period 1 (the first 21 days), the number of Cetaphil applications per subject will be provided using descriptive statistics.

Both observed exposure data (including eDiary) and derived exposure parameters will be provided in by-subject data listings.

In addition to the Safety Population, all exposure analyses will be performed on the ITT population as well.

7.1.1 Study Drug Exposure in the Maximal Use Arm

Study drug information will be provided in a by-subject data listing. Data collected from the Electronic Data Capture (EDC) as well as the subject eDiary will be provided.

Study drug compliance during the pharmacokinetic sampling period (Days 1 through 14) will be computed and presented in the listing.

7.2 Adverse Events

All adverse events (AEs) will be coded using the MedDRA v25.0 coding system and displayed in tables and data listings using system organ class (SOC) and preferred term. Missing and partial dates will be handled as described in Section 3.9.2.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any AE with onset after the first application of study drug through 30 days after the last study drug application, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related through 30 days after the last study drug application.

Adverse events will be summarized by subject incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given AE in both SOC and preferred term. The table will be sorted by descending frequency, based on the overall column of the data presentation.

Adverse events will be reported separately by event type; reporting of SOCs and preferred term will be as described above.

The number and percentage of subjects with any treatment-emergent adverse event (TEAE), with any TEAE assessed as related to study drug (possibly or probably), with any serious TEAE, any non-serious TEAE, with any serious TEAE potentially related to study drug, any non-serious TEAE potentially related to study drug, with any common (occurring in ≥5% of subjects) TEAE, or with any TEAE leading to study drug withdrawal will be provided. Additional tabulations will be provided for TEAEs by maximum severity, and TEAEs by strongest relationship to study drug.

All analyses above will be performed using both data presentations described in Section 3.9.3, where TEAEs will contribute to each summary only if they began in the corresponding period. For example, a TEAE starting during Periods 1 or 2 will be reported using the primary safety data presentation, and a TEAE starting during Period 3 will be reported using the open-label dosing data presentation.

Additionally, the proportion of subjects experiencing a TEAE through Week 12 will be reported along with exact binomial 95% confidence intervals, using the primary safety data presentation. The proportion of subjects experiencing a TEAE through Week 24 will be reported along with exact binomial 95% confidence intervals, using the open-label dosing data presentation.

All AEs occurring on-study will be listed in subject data listings. Listings will also be provided for the following: study drug related TEAEs, serious TEAEs, study drug related serious TEAEs, TEAEs leading to study drug withdrawal, and deaths.

7.2.1 Local Skin Reactions

The incidences of local skin reactions (LSRs) will be summarized for all visits according to the skin irritation scale (Grade 0 – none, Grade 1 – mild, Grade 2 – moderate, Grade 3 – severe) and type of reaction (burning/stinging, erythema, erosions, and edema). Changes from baseline will also be summarized for all visits and will be categorized into

'worsened' and 'same or improved' categories. For subjects reporting more than one occurrence of the same type of reaction, the most severe reaction will be used for the summary.

The proportion of subjects experiencing a LSR through Week 12 will be reported along with exact binomial 95% confidence intervals, using the primary safety data presentation. The proportion of subjects experiencing a LSR through Week 24 will be reported along with exact binomial 95% confidence intervals, using the open-label dosing data presentation. Additionally, the Week 12 analysis will be repeated, separating subjects that had ≥10 Cetaphil applications within the first 21 days, versus subjects that had <10 Cetaphil applications.

Additionally, the number and percentage of subjects who had suspected allergic contact dermatitis will be provided for all visits, along with exact binomial 95% confidence intervals. The number of subjects with confirmed cases of allergic contact dermatitis will be reported as well; subjects with confirmed cases are defined as those who had a suspected event reported, **and** allergic contact dermatitis reported as an AE.

A by-subject listing will be provided for all local skin reaction data.

7.2.2 Adverse Events and LSRs in the Maximal Use Arm

Adverse events and local skin reactions in subjects from the maximal use arm will be listed separately in a by-subject data listing. Event types will be provided to distinguish between study drug application site AEs and other AEs.

7.3 Clinical Laboratory Data

Clinical laboratory data will be expressed in international system of units (SI).

The actual value and change (both actual and percent) from baseline to each on-study evaluation will be summarized using descriptive statistics using the primary safety data presentation for each clinical laboratory parameter, including hematology, clinical chemistry, and qualitative urinalysis. Measurements that are unscheduled and that do not fall in a protocol-specified visit window will not contribute to the summary tabulations.

Laboratory tests will be classified in comparison to their reference range as: LN (Low Normal), LP (Low Panic), N (Normal), HN (High Normal), HP (High Panic), AB (Abnormal), SC (See Comment), and Blank when not used. Using these classifications, a shift table will be created to present any change from baseline in reference ranges in all laboratory tests across all post-baseline visits, including the worst post-baseline visit. Percentage of subjects will be calculated using the number of subjects with a baseline value and a non-missing value at the specified post-baseline visit as the denominator.

All laboratory data, including serology results, will be provided in by-subject data listings. A listing of all abnormal clinical laboratory results will be provided as well.

7.3.1 Laboratory Data in the Maximal Use Arm

Laboratory results from subjects in the maximal use arm will be listed separately.

7.4 Vital Signs

Vital sign parameters will include temperature, systolic and diastolic blood pressure, heart rate, and respiration rate. The actual value and change from baseline to each on-study evaluation will be summarized using descriptive statistics using the primary safety data presentation for each vital sign parameter. Measurements that are unscheduled and that do not fall in a protocol-specified visit window will not contribute to the summary tabulations.

Vital sign measurements and changes from baseline will be presented for each subject a data listing.

7.4.1 Vital Signs in the Maximal Use Arm

All vital sign data for subjects in the maximal use arm will be listed separately.

7.5 Physical Examination

Any new abnormalities in physical examination deemed clinically significant will be reported as an adverse event. All physical examination data will be presented in a by-subject data listing.

7.5.1 Physical Examination in the Maximal Use Arm

All physical examination data for subjects in the maximal use arm will be listed separately.

7.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary Version March 2022. Results will be tabulated by anatomic therapeutic class (ATC) and preferred term. Subjects will be counted only once by ATC and preferred term. Missing and partial dates will be handled as described in Section 3.9.3.

Concomitant medications are defined as any medication that did not end prior to first application of study drug. Prior medications consist of all medication that ended prior to the first application of study drug. If an end date is missing or the medication is ongoing, the medication will be considered both prior and concomitant.

A summary of prior medication used to treat CI will be provided as well.

The use of prior and concomitant medications will be included in a by-subject data listing. A listing of prohibited medications will also be provided; prohibited medications can be found in Table 7 of the study protocol.

7.6.1 Prior and Concomitant Medications in the Maximal Use Arm

Prior and concomitant medications used by subjects in the maximal use arm will be provided in a separate by-subject data listing.

8.0 CHANGES TO PLANNED ANALYSES

The following are changes between the protocol-defined statistical analyses and those presented in this statistical analysis plan:

- The key secondary objective of ascertaining the efficacy of TMB-001 0.05% at Week 12 using the VIIS-50 scaling score has been moved to an other secondary objectives. Related endpoints and analyses have been updated accordingly. This change was made per FDA feedback.
- The key secondary objective for pruritus, i.e. evaluating the effect of TMB-001 0.05% at Week 12 using the Itch-Numeric Rating Scale (I-NRS), was clarified to instead use the Worst Itch-Numeric Rating Scale (WI-NRS) rather than the I-NRS. This change was made per FDA feedback.

9.0 REFERENCES

Little, R. J. & D. B. Rubin (2019) Statistical Analysis with Missing Data, 3rd Edition (Vol. 793). *John Wiley & Sond, Inc*.

Nomura, K., H. Nakano, K. Umeki, K. Harada, A. Kon, K. Tamai, D. Sawamura & I. Hashimoto (1995) A study of the steroid sulfatase gene in families with X-linked ichthyosis using polymerase chain reaction. *Acta Derm Venereol,* 75**,** 340-2.

Ratitch, B., Lipkovich, I., & O'Kelly, M. (2013). Combining analysis results from multiply imputed categorical data. *PharmaSUG 2013-Paper SP03*, *2013*, 1-19.

Ratitch, B., & O'Kelly, M. (2011). Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures. *PharmaSUG 2011-Paper SP04*, *2011*, 1-10.

Takeichi, T. & M. Akiyama (2016) Inherited ichthyosis: Non-syndromic forms. *J Dermatol,* 43**,** 242-51.

Vahlquist, A., S. Blockhuys, P. Steijlen, K. van Rossem, B. Didona, D. Blanco & H. Traupe (2014) Oral liarozole in the treatment of patients with moderate/severe lamellar ichthyosis: results of a randomized, double-blind, multinational, placebo-controlled phase II/III trial. *Br J Dermatol,* 170**,** 173-81.

Vahlquist, A., A. Ganemo & M. Virtanen (2008) Congenital ichthyosis: an overview of current and emerging therapies. *Acta Derm Venereol,* 88**,** 4-14.

10.0 CHANGE HISTORY

Version	Date	Description of Changes
1.0	02 March 2023	Original Final Version
1.1	10 May 2023	Added the inclusion of a DSMB; Added the analysis of topline data after Week 12.
2.0	12 May 2023	Updated eCRF version referenced; Second Final Version
2.1	15 January 2024	Added additional subgroup analyses by gender and race; Added estimand framework for other secondary endpoints; Added use of multiple imputation for other secondary endpoints; Included smaller edits throughout the document.
2.2	16 February 2024	Added additional sensitivity analysis for primary and key secondary endpoints; Clarified primary methods of analysis for other secondary endpoints; Clarified the pruritus key secondary objective.
3.0	27 February 2024	Third Final Version

11.0 APPENDICES