Statistical Analysis Plan – Timber Pharmaceuticals, LLC

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

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1. SCOPE OF THE STATISTICAL ANALYSIS PLAN

This Statistical Analysis Plan is an adjunct to Timber Pharmaceuticals Protocol No. 235-9051-202 Amendment 1 dated 05 August 2020. The Statistical Analysis Plan details the procedures for the statistical methods used in the presentation and analysis of the clinical study data.

2. ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse event
ARCI-LI	Autosomal recessive congenital ichthyosis-lamellar ichthyosis
BSA	Body Surface Area
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	Congenital ichthyosis
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
DEC	Dose escalation committee
DLQI	Dermatology Life Quality Index
EOS	End of Study
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
I-NRS	Itch-Numeric Rating Scale
IWRS	Interactive Web Response System
IP	Investigational Product
ITT	Intent-to-treat
LSR	Local skin reaction
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
PP	Per-Protocol
QC	Quality control
RXLI	Recessive X-Linked ichthyosis
SAE	Serious adverse event
SAP	Statistical analysis plan
SDTM	Standard Data Tabulation Model

SOP	Standard operating procedure
VIIS	Visual Index for Ichthyosis Severity

3. RELEVANT AVANCE STANDARD OPERATING PROCEDURES AND GUIDANCES

The following Avance SOPs and regulatory guidances are relevant to this Statistical Analysis Plan:

- SOP-BIOM-0002 Clinical Data Analysis and Presentation
- SOP BIOM-0003 Blinding: Codes and Code Breaking
- SOP-BIOM-0004 Randomisation Generation
- SOP-BIOM-0009 Statistical Analysis Plans
- ICH: Statistical Principles for Clinical Trials (ICH E9, Current Step 4 version dated 5 February 1998)

4. INTRODUCTION

4.1. Study Overview

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

4.2. Study Objectives

- To investigate the efficacy of two concentrations of topically applied TMB-001 as a treatment for congenital ichthyosis (CI) of either the autosomal recessive congenital ichthyosis-lamellar ichthyosis (ARCI-LI) or RXLI subtypes.

- To investigate the safety of topically applied TMB-001.

4.3. Study Design

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

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

The duration of treatment will be 12 weeks.

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

4.4. Study Treatment

Investigational Product Name	Dosage of study medication?	Dose Frequency	Route of Administration
TMB-001	0.05%	BID	Topical
TMB-001	0.1%	BID	Topical
Vehicle Ointment (Control)	0%	BID	Topical

4.5. Sample Size

This is the first study of TMB-001 using the VIIS index. No formal power calculations were performed to establish sample size since there were no VIIS response data available. A sample size of 45 subjects (15 per treatment group) has been selected to provide initial data on VIIS response and to enable formal sample size calculations for future studies, as well as to assist in dose selection for Phase 3 study.

4.6. Study Endpoints

4.6.1 Efficacy Endpoints

4.6.1.1 Primary Efficacy:

- Proportion of subjects with VIIS "treatment success" (VIIS-50), which is defined as a 50% or greater decrease at Visit 6 (EOS) relative to Baseline in the sum of the scores for VIIS target sites that have a Baseline score of ≥ 3.

4.6.1.2 Key Secondary Efficacy:

- Proportion of subjects achieving IGA treatment success, where “treatment success” is defined as at least a 2-grade decrease in IGA severity score relative to Baseline at Visit 6 (EOS).

4.6.1.3 Other Secondary Efficacy:

- Time to achieve VIIS-50 (≥ 50% reduction in VIIS scaling score for body sites that had a Baseline score ≥ 3) that is maintained at the next observation.
- Changes in VIIS scaling score relative to Baseline at Visit 4 and Visit 5.
- Changes in percent BSA with CI relative to Baseline in the Treatment and Assessment Areas at Visit 3, Visit 4, Visit 5, and Visit 6 (EOS).
- Proportion of subjects with IGA “treatment success” at Visit 4, Visit 5, and Visit 6 (EOS).
- Proportion of subjects with an IGA score of 0 or 1 representing “cleared” or “almost cleared” at Visit 6 (EOS).

- Proportion of subjects with I-NRS "treatment success" where "success" is defined as at least a 4-point reduction in I-NRS relative to Baseline at Visit 6 (EOS).
- Change from Baseline in I-NRS score at Visit 6 (EOS).
- Change in DLQI from Baseline to Visit 6 (EOS).

4.6.2 Safety Endpoints

- Incidence (severity and causality) of any local skin reactions (LSRs) and systemic AEs.
- Number of subjects with presence (and severity) at each time point of the following LSRs: burning/stinging, erythema, erosions, and edema.
- Changes from Baseline in vital signs at Visit 6 (EOS).
- Changes from Baseline in clinical laboratory test results (chemistry, hematology, and urinalysis) at Visit 6 (EOS).
- AEs and SAE reported (severity, relatedness etc)

4.6.3 Exploratory Endpoints

- Time to 2 or more points decrease from baseline in IGA
- Time to achieve a score of 0 for both IGA and VIIS scaling
- Time to achieve a score of 1 for both IGA and VIIS scaling
- Kapa agreement analysis for VIIS and IGA scores at each visit
- Correlation of IGA scores and VIIS scaling at each visit
- Correlation of IGA scores and VIIS target sites scores at each visit
- Proportion of subjects with VIIS treatment success by body region
- Proportion of subjects with VIIS treatment success by genetic mutation
- Proportion of subjects with IGA treatment success by genetic mutation
- Proportion of subjects with VIIS treatment success by phenotype
- Proportion of subjects with IGA treatment success by phenotype
- Proportion of subjects with VIIS treatment success by drug/BSA ratio
- Proportion of subjects with IGA treatment success by drug/BSA ratio
- Proportion of subjects with VIIS treatment success by drug/BMI ratio
- Proportion of subjects with IGA treatment success by drug/BMI ratio
- Proportion of subjects with VIIS treatment success by drug/kg ratio
- Proportion of subjects with IGA treatment success by drug/kg ratio
- Proportion of subjects with VIIS treatment success by Baseline BSA Stratification
- Proportion of subjects with IGA treatment success by Baseline BSA Stratification
- Proportion of subjects with VIIS treatment success by OTC steroid cream usage
- Proportion of subjects with IGA treatment success by OTC steroid cream usage
- Proportion of subjects with VIIS treatment success by assessment medium
- Proportion of subjects with IGA treatment success by assessment medium
- Proportion of subjects with VIIS treatment success by drug interruption
- Proportion of subjects with IGA treatment success by drug interruption
- Proportion of subjects who meet both the primary and major secondary endpoint
- Proportion of subjects who achieve VIIS-$\geq$75 at target body sites

- Proportion of subjects who achieve VIIS-≥50 at non-target body sites
- Changes from Baseline in VIIS scaling, Active Vs Vehicle – MMRM analysis
- Changes from Baseline in I-NRS score, Active Vs Vehicle – MMRM analysis

5. DATA LISTINGS

5.1. Sources of Data

Data sets containing raw data will be provided by the Data Management group, extracted from the clinical study database of data entered into a Case Report Form (CRF). It is assumed that the database will contain the data from Screening through to the Follow-up Safety Visit of the study. Minimal information will be captured for screen failures.

Analysis datasets (SDTM and ADaM) will be generated from the data extracted from the study database, along with the following data entered separately or received from other sources:

- Randomization, from statistician responsible for its preparation
- Clinical laboratory safety data, provided by the clinical laboratory to Data Management at Avance Clinical

All data entered into the CRF or provided from other sources as described above will be presented (explicitly or implicitly) in data listings or figures as described in Appendix 1.

5.2. Randomization and Subject Identification Code

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

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

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

Subjects will be assigned a randomization number formatted, Rsnn where s is an indicator for the CI subtype (1 = ARCI-LI, 2 = RXLI) and nn is the random permutation of 01 - 45.

The listings for inclusion in an appendix to the clinical study report will be prepared after the study has been unblinded.

In the listings, subjects will be identified by subject number (assigned at randomization), with treatment as a secondary grouping identifier. Screening number will be shown only on the listing of informed consent data and screen failure data.

5.3. Maintaining the Study Blind

In this double-blind study, all personnel involved, i.e., physicians, site staff, and subjects 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.

5.4. Assessment Time Point Identifiers

In the data listings for the report, scheduled assessment time points will be identified as follows:

- Scheduled safety assessments will be identified by treatment group, study day, and also nominal study time point, where relevant.
- Assessments at Screening and End of Study will be identified as such for both study day and time-point, as appropriate.

5.5. Data Derived by Calculation

The following data fields for inclusion in the data listings will be derived by calculation as per clinical data interchange standards consortium (CDISC) standard:

- Treatment-emergent Indicator for adverse event, assigned as
  Treatment-Emergent if
  (Onset Date + Onset Time) >= (Date of First Dose + Time of First Dose)

  Non Treatment-Emergent if
  (Onset Date + Onset Time) < (Date of First Dose + Time of First Dose)
- Adverse event time since first dose (in days, to two decimal places), calculated as
  (Onset Date + Onset Time) – (Date of First Dose + Time of First Dose)

AE Duration:

- Adverse event duration (in days, to two decimal places), calculated as
  (Resolution Date + Resolution Time – Onset Date - Onset Time)

Safety Assessments Change from Baseline:

- Baseline for Vital Signs and serum clinical laboratory parameters will be the most recent scheduled assessment prior to first dose

Clinical Safety Laboratory Assessments:

- If a clinical laboratory result is above the upper limit of normal, then Out of Range flag will be set to "H"

- If a clinical laboratory result is below the lower limit of normal, then Out of Range flag will be set to "L"
- Clinical Laboratory parameters that are outside the reference range and assessed by the Principal Investigator as clinically significant will be identified as "Abnormal CS"
- Clinical Laboratory parameters that are outside the reference range and assessed by the Principal Investigator as not clinically significant will be identified as "Abnormal NCS"

5.6. Handling of Missing Data

5.6.1. Efficacy Missing Data Rules:

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

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

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

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

4) by assuming that subjects with missing data are treatment failures ("non-responder")

5.6.2. Adverse Events Missing Data Rules:

For adverse events with unknown intensity (severity) or unknown relationship to study treatment, these will be imputed as follows:

- If the intensity (severity) of an adverse event is unknown/missing, the intensity will be imputed for the summary of adverse events as being the highest intensity that is not immediately life-threatening or resulting in death, i.e. "Severe".
- If the relationship to investigational product of an adverse event is unknown/missing, and the adverse event onset occurred after first dose, or if onset date/time is unknown and it cannot be determined if onset occurred prior to dosing the relationship will be imputed for the summary of adverse events as related.

For adverse events, where either the onset time or resolution time is unknown, time since first dose and duration will be imputed as follows:

- If onset date is unknown, and it cannot be confirmed that onset was prior to the start of dose administration, then the AE will be classified as treatment-emergent, with unknown time since first dose.

- If either the date of onset or the date of resolution is unknown, then duration will be shown as unknown.
- If onset time is unknown:
  - If the date of onset is known to be the date of first dose administration, and it is confirmed by a CRF comment or communication with the site that onset was prior to the start of dose administration, then the AE will be classified as not treatment-emergent.
  - If the date of onset is known to be same as the date of first dose administration, and it is confirmed by a CRF comment or communication with the site that onset was after the start of dose administration, then the AE will be classified as treatment-emergent and the time since first dose will be shown on the listing as "<1" day.
  - If the date of onset is known to be later than the date of first dose administration, then Time since first dose will be determined as the number of days since first dose, shown on the listing as "~n" days, where n is the number of days difference between the date of dose administration and the date of onset.
- If either the onset time or resolution time is unknown:
  - If the date of onset and the date of resolution are known to be the same, then Duration will be shown on the listing as "<1" day.
  - If the date of onset and the date of resolution are known and are different, then Duration will be determined as the number of days difference between the date of onset and the date of resolution, shown on the listing as "~n" days.

5.6.3. Baseline for safety assessments:

- Missing values for safety assessments will not be imputed. If change from baseline is to be determined and the pre-dose baseline assessment is missing, then the previous scheduled result (e.g. Screening) will be used as the baseline. However, if the baseline is missing due to technical reasons and a subsequent unscheduled pre-dose assessment is used to confirm eligibility, this unscheduled assessment may be used as baseline.

5.7. Use of Abbreviations

Any abbreviations used in data listings will be included in the key in a footnote, as appropriate.

6. ANALYSIS POPULATIONS

6.1. Intent-to-Treat (ITT) Population

All randomized subjects who received at least one dose of study medication will be included in the ITT population. Subjects will be analysed according to the treatment they are planned to receive according to the randomization schedule. The ITT population will be used for the analysis and presentation of all efficacy data.

6.2. Per-Protocol (PP) Population

Subset of the ITT population consisting of subjects who 1) meet all inclusion/exclusion criteria that would affect the treatment evaluation, 2) apply ≥ 80% but ≤ 120% of the planned doses of study treatment, 3) who had a VIIS measurement at Visit 6 (EOS), and 4) have no major protocol violations that would affect the treatment evaluation. Subjects will be analysed according to the treatment they are planned to receive according to the randomization schedule. All efficacy data will be analysed using the PP population.

6.3. Safety Population

All subjects randomly assigned to study treatment and who take at least 1 dose of study medication will be included in the Safety Population. Subjects will be analysed according to the treatment they actually receive. Safety data will be presented for all subjects in the safety analysis set and summarised by dose level / treatment group.

Subject disposition and background data, including demographics, relevant background and participation data, will be presented for all subjects in the safety analysis set.

Subjects who are assigned a randomization number but withdraw prior to dosing will not be included in the safety analysis set. Available details of their participation and reason for withdrawal will be listed separately.

7. SUBJECT DISPOSITION/BACKGROUND DATA

7.1. Subject Disposition

Subject disposition and administration procedures recorded in the CRF are as follows:

- Written informed consent
- Randomization
- Administration of IP
- Study completion /discontinuation
- Protocol deviations
- Additional comments

Details of participation and inclusion in analysis populations will be listed by subject. Completion status will be summarised by dose level / treatment group.

Details of administration of IP will be listed by subject. Exposure to IP will be summarised by dose level / treatment group. Descriptive statistics will be used to summarize study treatment compliance for the ITT population. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% but no more than 120% of the expected number of applications or dose.

Protocol deviations will be listed by subject.

Screen failures will be listed by subject. Demography, screen failure details, eligibility criteria, and any SAEs will be listed for screen failures.

7.2. Baseline and Eligibility Assessments

Baseline and eligibility assessments are as follows:

- Demographic details
- Medical and surgical history
- Physical examination
- Eligibility
- Genetic testing
- Serology (HIV)
- Urine pregnancy tests
- Assessments at screening and up to pre-dose baseline of safety assessments performed throughout the study, including physical examinations and vital signs

7.3. Baseline Data Analysis

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

8. SAFETY DATA

8.1. Safety Assessments

Safety assessments are as follows:

- Adverse events and concomitant medications used:
  - Continuous monitoring throughout the study period
- Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured at Visit 1 (Screening) and Visit 6 (EOS).
- Clinical laboratory tests:
  - Clinical Chemistry: Blood Urea Nitrogen, Creatinine, Glucose (Fasting), Potassium, Sodium, Calcium, Aspartate aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT), Alanine aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT), Alkaline Phosphatase, Total and Direct Bilirubin and Total Protein
  - Hematology: Platelet Count, Red Blood Cell (RBC) Count, Haemoglobin, Hematocrit, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), % Reticulocytes, lymphocytes, monocytes, eosinophils, basophils, neutrophils
  - Routine Urinalysis: Specific Gravity, pH, Glucose, Protein, Blood, Ketones, (Bilirubin, Urobilinogen, Nitrite, Leukocyte Esterase) by Dipstick, Microscopic Examination (if Blood or Protein Is Abnormal)

- Serology: human immunodeficiency virus [HIV] Antibody
- Drug and alcohol screen: Opiates, methadone, cocaine, amphetamines (including ecstasy), cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol
- Pregnancy test (Women of Childbearing Potential): Urine Human Chorionic Gonadotropin (hCG) Pregnancy Test

- Physical examination: A brief physical examination will be performed at Visit 1 (Screening). Abbreviated examination/ subject disposition will be conducted at Visit 2 (Baseline) to identify any changes since the Screening visit and at Visit 6 EOS to assess for any changes during the study. The examination will evaluate head and neck, dermatological, cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait body assessments. Abnormalities at Visit 1 (Screening) and Visit 2 (Baseline) prior to treatment will be recorded as medical history. Any new or worsening abnormalities at Visit 6 (EOS) will be recorded as AEs.
- Local Skin Reactions (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 will be evaluated at every study visit (except Screening), using a 4-point ordinal scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

8.2. Safety Data Presentation and Analysis

All clinical safety and tolerability data will be listed for each subject.

Safety data will be presented for all subjects in the safety analysis set and summarised by dose level / treatment group.

Safety data will be summarized descriptively in tabular form. Summaries of key safety data assessed over time may also be presented in graphical form, as appropriate. Where summaries include changes from baseline, the relevant baseline value will be determined as described in Section 5.5 above.

All treatment-emergent adverse events reported in this study will be presented using MedDRA terms, as coded per the Data Management Plan. AEs and SAEs with onset following administration of the investigational product will be summarised by dose level / treatment, grouped according to system organ class and preferred term, and tabulated with descriptive statistics, where appropriate, for number of subjects and number of AEs per category, for all AEs and for AEs deemed drug-related. AEs will also be summarised by severity and by relationship to investigational product. Where a subject has more than one AE for the same MedDRA category, the subject will be counted only once, for the AE of highest severity or least favourable relationship.

Prior and concomitant medication will be coded using the WHO Drug Dictionary (WHODrug), as coded per the Data Management Plan. The number and percentage of subjects taking prior medication, and concomitant medication will be summarised using frequency tables according to WHO Drug ATC Level 1 Code Description and the WHO Drug Dictionary Preferred Name. If a subject has more than one prior or concomitant medication coded to the same category, the subject will be counted only once.

Clinical laboratory parameters will be tabulated and summarised by dose level / treatment group and study time point. A summary of changes from baseline will also be presented for clinical laboratory parameters. Medical assessments of blood and urine parameters will be summarised by treatment group and study time point. Individual subject profiles will be presented for any laboratory parameters with at least one post-dose value outside the laboratory's reference ranges and deemed clinically significant.

Vital signs (systolic/diastolic blood pressure, heart rate, body temperature and respiratory rate) will be tabulated and summarised by dose level / treatment and study time point, separately for supine and standing. A summary of changes from baseline will also be presented.

Changes from screening or previous visit in physical examination findings will be listed for each subject. It is noted that any untoward findings identified on physical and neurological examinations after the start of administration of the study medication will be captured as an adverse event if those findings meet the definition of an adverse event as defined in the protocol.

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

9. EFFICACY DATA

9.1. Efficacy Data Presentation

9.1.1. VIIS

VIIS scores will be listed, for each body area, per subject, per visit. Body areas will be identified as target or non-target and this information will be provided in the individual listing as well. Descriptive statistics (including frequencies and percentages) for observed, change from Baseline values in VIIS scaling at each visit, success rate, as well as a shift table will be presented by treatment group for each CI subtype and overall. VIIS scaling is defined as the average of the severity scores for the VIIS body areas, where the numerator is the sum of the severity scores and denominator is the number of body areas assessed at that visit. Success is defined as a $\geq$ 50% reduction at Visit 6 relative to Baseline in the sum of VIIS scores for target body sites that had a Baseline score $\geq$ 3. That is, a participant is flagged as treatment success if, at Visit 6 (or EOS), the sum of the VIIS scores for the same target body sites identified at Baseline is $\geq$ 50% lower than the sum of VIIS scores for these target body sites at Baseline. Results from Cochran-Mantel-Haenszel test at Visit 6 (EOS) will be presented together with corresponding 95% confidence intervals. Time from baseline to treatment success will be estimated using KM analysis and individual results will be listed and summarized using descriptive statistics.

9.1.2. IGA

IGA scores will be listed per subject, per visit. Descriptive statistics (including frequencies and percentages) for observed, change from Baseline values in IGA at each

visit, success rate, as well as a shift table will be presented by treatment group for each CI subtype and overall. Success is defined as a at least 2-grade decrease in severity score relative to baseline. Time from baseline to treatment success will be estimated using KM analysis and individual results will be listed and summarized using descriptive statistics.

9.1.3. I-NRS

I-NRS scores at each visit and change from baseline at each visit will be listed per subject for Visit 2 (Baseline), Visit 5, and at Visit 6 (EOS). Descriptive statistics (including frequencies and percentages) for observed and change from Baseline values in I-NRS at each visit, success rate as well as a shift table will be presented by treatment group for each CI subtype and overall. Success is defined as ≥ 4-point reduction from Baseline. Results from Cochran-Mantel-Haenszel test at Visit 6 (EOS) will be presented together with corresponding 95% confidence intervals.

9.1.4. DLQI

DLQI scores will be listed per subject for Visit 2 (Baseline), Visit 5, and at Visit 6 (EOS). Descriptive statistics (including mean, median, SD, min, and max) for observed and change from Baseline values in DLQI at each visit will be presented by treatment group for each CI subtype and overall. Subgroup analysis using descriptive statistics for observed and change from baseline values in DLQI at each visit will be performed on subjects with DLQI less than 10 and greater or equal to 10 at baseline. The same subgroup analysis will be performed for CDLQI values, where the subgroups will be: a score less than 13 on CDLQI at baseline vs score of 13 or more on CDLQI at baseline. Proportion of subjects with DLQI improvement of 4 or greater points from baseline will be described using frequency tables.

9.1.5. Percent BSA affected

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

9.2. Efficacy Analysis

Efficacy analyses will be performed on both the ITT and PP populations with the ITT population considered primary.

9.2.1. Primary Efficacy Endpoint

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

9.2.2. Secondary Efficacy Endpoints

- The proportion of subjects achieving IGA treatment success will be the key secondary endpoint. The IGA score will be dichotomized to "treatment success" or

"treatment failure" where "treatment success" is defined as at least a 2-grade decrease in severity score relative to Baseline. Active treatment will be compared with vehicle at Visit 6 (EOS) using the CMH test stratified by CI subtype and 95% confidence intervals will be calculated for the difference in proportions for the treatment groups.

Other Secondary Endpoints:

- The time to achieve VIIS-50 (≥ 50% reduction in VIIS scaling score for body sites that had a Baseline score ≥ 3) that is maintained at the next observation. If VIIS-50 is first achieved at Visit 6 (EOS), then the endpoint is considered to have been met. A time to event analysis will be performed using the Kaplan-Meier (K-M) method and log rank test to compare active treatment with vehicle. The results from K-M analysis will be tabulated as well as graphically presented.

- Changes in VIIS scaling score relative to Baseline at Visit 4 and Visit 5:
  The treatment groups will be compared with respect to the change from Baseline using mixed model of repeated measures (MMRM) including terms for treatment, visit, treatment by visit interaction, and the Baseline VIIS scaling score serving as the covariate. VIIS scaling score is defined as the average score of grades for all body areas assessed at that visit. From the model, the active to vehicle treatment differences will be estimated. Additionally, two-sided confidence intervals will be provided.

- Proportion of subjects with IGA "treatment success" at Visit 4, Visit 5, and Visit 6 (EOS):
  Descriptive statistics (including frequencies and percentages) for IGA success rate will be presented by treatment group for each CI subtype and overall. Success is defined as a ≥ 2-point reduction in IGA score from Baseline.

- Proportion of subjects with IGA score representing "cleared" or "almost cleared" at Visit 6 (EOS):
  Descriptive statistics (including frequencies and percentages) for IGA scores representing "cleared" or "almost cleared" will be presented by treatment group for each CI subtype and overall. "Cleared" or "Almost cleared" is defined as an IGA score of 0 or 1.

- Changes in percent BSA relative to Baseline with CI in the Treatment/Assessment Areas at Visit 3, Visit 4, Visit 5, and Visit 6 (EOS):
  Descriptive statistics (including mean, median, SD, min, and max) for observed and change from Baseline values in percent BSA at each visit will be presented by treatment group for each CI subtype and overall.

- Change from Baseline in Itch-Numeric Rating Scale (I-NRS) score at Visit 6 (EOS):
  The treatment groups will be compared with respect to the change from Baseline using mixed model of repeated measures (MMRM) including terms for treatment, visit, treatment by visit interaction, and the Baseline I-NRS value serving as the covariate. From the model, the active to vehicle treatment differences will be estimated. Additionally, two-sided confidence intervals will be provided.

- Change in DLQI from Baseline to Visit 6 (EOS):
  Descriptive statistics (including mean, median, SD, min, and max) for observed and change from Baseline values in DLQI and CDLQI at each visit will be presented by treatment group for each CI subtype and overall.

9.2.3. Exploratory Endpoints

- Time to 2 or more points decrease from baseline in IGA:
  A time to event analysis will be performed using the Kaplan-Meier (K-M) method and log rank test to describe the time to 2 or more points decrease from baseline in IGA.

- Time to achieve a score of 0 for both IGA and VIIS scaling:
  A time to event analysis will be performed using the Kaplan-Meier (K-M) method and log rank test to describe the time to achieve a score of 0 for both IGA and VIIS scaling.

- Time to achieve a score of 1 for both IGA and VIIS scaling:
  A time to event analysis will be performed using the Kaplan-Meier (K-M) method and log rank test to describe the time to achieve a score of 1 for both IGA and VIIS scaling.

- Kappa agreement analysis for VIIS and IGA scores at each visit:
  Kappa coefficients will be calculated for VIIS scaling and IGA score agreement at each visit.

- Spearman and Pearson Correlation coefficient will be calculated between VIIS scaling scores and IGA scores, and between VIIS target sites scores and IGA at each visit.

- Proportion of subjects with VIIS treatment success by body region:
  If data allows, proportion of subjects with VIIS treatment success will be compared between treatment groups in cases where the same body areas have been treated. Descriptive statistics (including frequencies and percentages) VIIS treatment success will be presented by body region.

- Proportion of subjects with VIIS treatment success by genetic mutation:
  Descriptive statistics (including frequencies and percentages) for VIIS treatment success will be presented by genetic mutation.

- Proportion of subjects with IGA treatment success by genetic mutation:
  Descriptive statistics (including frequencies and percentages) for IGA treatment success will be presented by genetic mutation.

- Proportion of subjects with VIIS treatment success by phenotype:
  Descriptive statistics (including frequencies and percentages) for VIIS treatment success will be presented by phenotype.

- Proportion of subjects with IGA treatment success by phenotype:

Descriptive statistics (including frequencies and percentages) for IGA treatment success will be presented by phenotype.

- Proportion of subjects with VIIS treatment success by drug/BSA ratio:
  Drug/BSA ratio will be calculated for each participant and values will be flagged according to median ratio as above or below median. Descriptive statistics (including frequencies and percentages) for VIIS treatment success will be presented by drug/BSA ratio.

- Proportion of subjects with IGA treatment success by drug/BSA ratio:
  Drug/BSA ratio will be calculated for each participant and values will be flagged according to median ratio as above or below median. Descriptive statistics (including frequencies and percentages) for IGA treatment success will be presented by drug/BSA ratio.

- Proportion of subjects with VIIS treatment success by drug/BMI ratio:
  Drug/ BMI ratio will be calculated for each participant and values will be flagged according to median ratio as above or below median. Descriptive statistics (including frequencies and percentages) for VIIS treatment success will be presented by drug/ BMI ratio.

- Proportion of subjects with IGA treatment success by drug/BMI ratio:
  Drug/ BMI ratio will be calculated for each participant and values will be flagged according to median ratio as above or below median. Descriptive statistics (including frequencies and percentages) for IGA treatment success will be presented by drug/ BMI ratio.

- Proportion of subjects with VIIS treatment success by drug/kg ratio:
  Drug/ kg ratio will be calculated for each participant and values will be flagged according to median ratio as above or below median. Descriptive statistics (including frequencies and percentages) for VIIS treatment success will be presented by drug/ kg ratio.

- Proportion of subjects with IGA treatment success by drug/kg ratio:
  Drug/ kg ratio will be calculated for each participant and values will be flagged according to median ratio as above or below median. Descriptive statistics (including frequencies and percentages) for IGA treatment success will be presented by drug/ kg ratio.

- Proportion of subjects with VIIS treatment success based on BSA Stratification:
  Participants will be stratified according to Baseline BSA data. Descriptive statistics (including frequencies and percentages) of VIIS treatment success will be presented by BSA stratification.

- Proportion of subjects with IGA treatment success based on BSA Stratification:
  Participants will be stratified according to Baseline BSA data. Descriptive statistics (including frequencies and percentages) of VIIS treatment success will be presented by BSA stratification.

- Proportion of subjects with VIIS treatment success by OTC steroid cream usage:
  Descriptive statistics (including frequencies and percentages) for VIIS treatment success will be presented by OTC steroid cream.

- Proportion of subjects with IGA treatment success by OTC steroid cream usage:
  Descriptive statistics (including frequencies and percentages) for IGA treatment success will be presented by OTC steroid cream.

- Proportion of subjects with VIIS treatment success by assessment medium:
  Descriptive statistics (including frequencies and percentages) for VIIS treatment success will be presented by assessment medium (online vs onsite).

- Proportion of subjects with IGA treatment success by assessment medium:
  Descriptive statistics (including frequencies and percentages) for IGA treatment success will be presented by assessment medium (online vs onsite).

- Proportion of subjects with VIIS treatment success by drug interruption:
  If data allows, descriptive statistics (including frequencies and percentages) for VIIS treatment success will be presented by the following drug interruption categories: frequency, duration, location and action outcome of the drug interruption.

- Proportion of subjects with IGA treatment success by drug interruption:
  If data allows, descriptive statistics (including frequencies and percentages) for IGA treatment success will be presented by the following drug interruption categories: frequency, duration, location and action outcome of the drug interruption.

- Proportion of subjects who meet both the primary and major secondary endpoint:
  Descriptive statistics (including frequencies and percentages) of subjects who meet both the primary and major secondary endpoint.

- Proportion of subjects who meet VIIS 75 scaling at visit 6:
  Descriptive statistics (including frequencies and percentages) of subjects who meet VIIS 75 (≥ 75% reduction in VIIS scaling score for VIIS target body sites that had a Baseline score ≥ 3) at visit 6.

- Proportion of subjects with VIIS "treatment success" (VIIS-50) at non-target body sites:
  In cases where VIIS body areas have been identified as non-target sites, and had a baseline score of ≥ 3, the proportion of subjects at Visit 6 (EOS) relative to Baseline with 50% or greater decrease in sum of VIIS scaling score in non-target sites will be presented using frequency statistics.

- Changes from Baseline in VIIS score, Active Vs Vehicle
  Active treatment groups will be combined into one group and compared to vehicle group with respect to the change from Baseline using mixed model of repeated measures (MMRM) including terms for treatment, visit, treatment by visit interaction, and the Baseline VIIS value serving as the covariate.

- Changes from Baseline in I-NRS score, Active Vs Vehicle

Active treatment groups will be combined into one group and compared to vehicle group with respect to the change from Baseline using mixed model of repeated measures (MMRM) including terms for treatment, visit, treatment by visit interaction, and the Baseline I-NRS value serving as the covariate.

10. PHARMACOKINETIC/PHARMACODYNAMIC DATA

Pharmacokinetic/Pharmacodynamic parameters will not be evaluated in this study.

11. CHANGES FROM THE ANALYSIS PLANNED IN THE PROTOCOL

There are no changes from the planned analysis described in the protocol.

12. DATA LISTINGS AND SUMMARY TABLES

12.1. Interim/Preliminary Data Analysis

No interim analyses are planned.

12.2. Listings and Tables for Clinical Study Report

The data listings and summary tables, and associated figures, planned to be generated from the study data are listed in Appendix 1 and Appendix 2, respectively. The numbering and titles may vary in the final presentation, depending on the amount of data to be presented.

Listings, tables and figures will be provided to the Sponsor in a form suitable for inclusion as appendices to the Clinical Study Report, in RTF or PDF format. The layout will be landscape A4 size, with a margin of 1 inch. The default font for listings and tables will be Courier New 8 pt.

In the summary tables other than those included in the main text of the report, special characters and formatting will not be used. For example, units will be shown as ug (µg) and m^2 (m²), if/where these example units are applicable.

Data in listings will be ordered by treatment, then subject, then date/time.

Data to be presented graphically includes: Visual Index for Ichthyosis Severity success rate, Time to VIIS-50 - Kaplan-Meier Analysis, Investigator's Global Assessment success rate and Itch- Numeric Rating Scale success rate. All of these efficacy endpoints will be graphically presented using both, ITT and PP population.

12.3. Data Transfer to the Study Sponsor

At the conclusion of the study, Avance will provide the Sponsor with an electronic copy of the listings, tables and graphs, along with analysis data sets in SAS transport format and XPT format. This may be provided by email or by upload, as determined by the Sponsor.

Details of the statistical analyses will be retained in the Avance study file for reference.

13. GENERAL CONSIDERATIONS FOR DATA MANAGEMENT AND ANALYSIS

13.1. Analysis Packages

SAS 9.4 or higher (SAS Institute Inc., Cary, NC, USA) will be used for generating data listings and summary tables and associated figures, and for performing statistical analysis.

13.2. Electronic Data Management

All listings, tables and figures for inclusion in the appendices of the clinical study report will be generated using SAS programs.

A copy of final listings, tables and figures will be retained in the Avance internal study file. A tracking log will be maintained detailing the date and initials of the staff member responsible for generating each listing, table or figure, and the staff member conducting the quality control review. Any erroneous results identified during subsequent checking process will be corrected by update of the SAS program, and the document recreated and then re-checked. To ensure an accurate data trail is maintained, corrections to electronic documents will be included on the tracking log, detailing the correction along with the date of the new version as well as the initials of the staff member responsible for the change and the verifying staff member. If statistical analysis is repeated with a modified data set, the new data produced will be saved as a new file.

13.3. Archiving

At the conclusion of the study, the final listings, tables and figures and associated QC documentation will be archived along with the SDTM (SDTM v1.7 and SDTMIG v3.3) and ADaM (ADaM v2.1 and ADaMIG v1.1) data sets, programs and CDISC documentation. Copies will be retained in the Avance study file for a minimum of 15 years, and in the Avance secure archives in accordance with Avance standard operating procedures.

Appendix 1: Planned Data Listings

The following listings and figures of individual subject data are planned to be generated for this study, however the numbering and titles may vary depending on CDISC datasets:

Listing/Figure #	Listings/Figure Title
Subject Participation	
Listing 16.2.1.1	Informed Consent
Listing 16.2.1.2	Subjects who did not meet Inclusion and Exclusion Criteria
Listing 16.2.1.3	Study Completion / Discontinuation
Listing 16.2.1.4	Screen Failures
Listing 16.2.1.5	Randomization
Protocol Deviations	
Listing 16.2.2.1	Protocol Deviations
Listing 16.2.2.2	Additional Comments
Analysis Populations	
Listing 16.2.3.1	Analysis Set Inclusion by Subject
Demographics and Baseline Information	
Listing 16.2.4.1	Demographics (Safety Population)
Listing 16.2.4.2	Demographics (ITT)
Listing 16.2.4.3	Demographics (PP)
Listing 16.2.4.4	Genetic Testing Confirmation (Safety Population)
Listing 16.2.4.5	Genetic Testing Confirmation (ITT)
Listing 16.2.4.6	Genetic Testing Confirmation (PP)
Listing 16.2.4.7	Assessment Medium (Safety Population)
Listing 16.2.4.8	Assessment Medium (ITT)
Listing 16.2.4.9	Assessment Medium (PP)
Listing 16.2.4.10	Percent BSA with Active Congenital Ichthyosis (Safety Population)
Listing 16.2.4.11	Percent BSA with Active Congenital Ichthyosis (ITT)
Listing 16.2.4.12	Percent BSA with Active Congenital Ichthyosis (PP)
Listing 16.2.4.13	Medical and Surgical History (Safety Population)
Listing 16.2.4.14	Medical and Surgical History (ITT)
Listing 16.2.4.15	Medical and Surgical History (PP)
Listing 16.2.4.16	Serology Screening (Safety Population)
Listing 16.2.4.17	Serology Screening (ITT)
Listing 16.2.4.18	Serology Screening (PP)
Listing 16.2.4.19	Drug and Alcohol Screening (Safety Population)
Listing 16.2.4.20	Drug and Alcohol Screening (ITT)
Listing 16.2.4.21	Drug and Alcohol Screening (PP)
Listing 16.2.4.22	Urine Pregnancy Tests (Safety Population)
Listing 16.2.4.23	Urine Pregnancy Tests (ITT)
Listing 16.2.4.24	Urine Pregnancy Tests (PP)
Listing 16.2.4.25	Height and Weight (Safety Population)

Listing/Figure #	Listings/Figure Title
Listing 16.2.4.26	Height and Weight (ITT)
Listing 16.2.4.27	Height and Weight (PP)
Listing 16.2.4.28	Drug/Weight Ratios (Safety Population)
Listing 16.2.4.29	Drug/Weight Ratios (ITT)
Listing 16.2.4.30	Drug/Weight Ratios (PP)
Listing 16.2.4.31	Prior and Concomitant Medications (Safety Population)
Listing 16.2.4.32	Prior and Concomitant Medications (ITT)
Listing 16.2.4.33	Prior and Concomitant Medications (PP)
Treatment Administration	
Listing 16.2.5.1	Study Drug Administration
Listing 16.2.5.2	Investigation Product (IP) Compliance
Listing 16.2.5.3	Drug Interruption Details
Listing 16.2.5.4	Pre-dose Eligibility Reviews
Efficacy Data	
Listing 16.2.6.1	Visual Index for Ichthyosis Severity
Listing 16.2.6.2	Investigator's Global Assessment
Listing 16.2.6.3	VIIS – Kappa Coefficients
Listing 16.2.6.4	IGA – Kappa Coefficients
Listing 16.2.6.5	VIIS Scaling Scores and IGA– Correlation Coefficients
Listing 16.2.6.6	VIIS Target Sites Scores and IGA– Correlation Coefficients
Listing 16.2.6.7	Itch - Numeric Rating Scale
Listing 16.2.6.8	Dermatology Quality of Life Index - Adults
Listing 16.2.6.9	Dermatology Quality of Life Index - Children
Safety Data (Adverse Events)	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Serious Adverse Events
Listing 16.2.7.3	Incidence (severity and causality) of local skin reactions (LSRs) and systemic AEs
Safety Data (Clinical Laboratory Evaluations)	
Listing 16.2.8.1	Clinical Laboratory Blood Sample Collection
Listing 16.2.8.2	Hematology Results
Listing 16.2.8.3	Clinical Chemistry Results
Listing 16.2.8.4	Clinical Laboratory Urine Sample Collection
Listing 16.2.8.5	Urinalysis Results
Safety Data (Other Assessments)	
Listing 16.2.9.1	Vital Signs
Listing 16.2.9.2	Vital Signs, Calculated Changes from Baseline
Listing 16.2.9.3	Local Skin Reactions
Listing 16.2.9.4	Physical Examinations

Appendix 2: Planned Summary Tables

The following summary tables are planned to be produced, however the table numbers and titles may vary, depending on the amount of data to be presented:

14.1 Subject Data Summaries

Table 14.1.1	Summary of Study Disposition
Table 14.1.2	Summary of Demographics (Safety Population)
Table 14.1.3	Summary of Demographics (ITT)
Table 14.1.4	Summary of Demographics (PP)
Table 14.1.5	Summary of Treatment / Total Dose Administered (Safety Population)
Table 14.1.6	Summary of Treatment Compliance (ITT)
Table 14.1.7	Summary of Concomitant Medication (ITT)

14.2 Efficacy Data Summaries

Table 14.2.1.1.1	Visual Index for Ichthyosis Severity – Change From Baseline (ITT)
Table 14.2.1.1.2	Visual Index for Ichthyosis Severity – Change From Baseline (PP)
Table 14.2.1.2.1	Visual Index for Ichthyosis Severity – Shift Table (ITT)
Table 14.2.1.2.2	Visual Index for Ichthyosis Severity – Shift Table (PP)
Table 14.2.1.3.1	Visual Index for Ichthyosis Severity – Success Rate (ITT)
Figure 14.2.1.3.1	Visual Index for Ichthyosis Severity – Success Rate (ITT)
Table 14.2.1.3.2	Visual Index for Ichthyosis Severity – Success Rate (PP)
Figure 14.2.1.3.2	Visual Index for Ichthyosis Severity – Success Rate (PP)
Table 14.2.1.4.1	Visual Index for Ichthyosis Severity – Success Rate – CMH analysis at Visit 6 (EOS) (ITT)
Table 14.2.1.4.2	Visual Index for Ichthyosis Severity – Success Rate – CMH analysis at Visit 6 (EOS) (ITT) (Best Case Analysis)
Table 14.2.1.4.3	Visual Index for Ichthyosis Severity – Success Rate – CMH analysis at Visit 6 (EOS) (ITT) (Worst Case Analysis)
Table 14.2.1.4.4	Visual Index for Ichthyosis Severity – Success Rate – CMH analysis at Visit 6 (EOS) (ITT) (LOCF)
Table 14.2.1.4.5	Visual Index for Ichthyosis Severity – Success Rate – CMH analysis at Visit 6 (EOS) (ITT) (Non-Responder Analysis)
Table 14.2.1.4.6	Visual Index for Ichthyosis Severity – Success Rate – CMH analysis at Visit 6 (EOS) (PP)
Table 14.2.1.5.1	Changes from Baseline in VIIS score relative to Visit 4 and Visit 5 – MMRM analysis (ITT)
Table 14.2.1.5.2	Changes from Baseline in VIIS score relative to Visit 4 and Visit 5 – MMRM analysis (PP)

14.3 Safety Data Summaries

14.3.1 Adverse Event Summaries

14.3.2 Deaths, Other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Event

14.3.4 Clinical Laboratory Assessments

14.3.5 Vital Signs

14.3.6 Other Measurements

Table 14.3.6.2 Physical Examination