Statistical Analysis Plan (SAP)

Validation of a novel composite of skin biomarkers as a primary outcome measure for evaluating the safety of treatments for atopic dermatitis: a randomized controlled trial (phase 2) comparing the effects of crisaborole 2% ointment to betamethasone valerate 0.1% cream on skin structure and function in participants with atopic dermatitis.

Skin bioMARkers for atopic eczema Therapy evaluation

NCT04194814

Contents

Abbreviations 3
1. Introduction: 4
2. Study Methods 4
2.1 Study Design 4
2.2 Randomisation 5
2.3 Sample size: 5
2.4 Timelines 6
3. Data Collection: 6
4. Analysis Objectives: 7
4.1 Primary objective: 7
4.2 Secondary objective: 7
4.3 Exploratory objectives: 7
5. Analysis Sets and Protocol Deviations 8
6. Endpoints and Covariates 8
6.1 Primary endpoints 8
6.2 Secondary endpoints 8
6.3 Exploratory endpoints: 9
6.4 Variables 9
7. Statistical Analyses 11
7.1 Primary Analysis 11
7.2 Secondary Analysis 11
7.3 Exploratory Analysis 12
7.4 Adverse event data: 12
7.5 Multiplicity considerations 12
7.6 Missing and unusual data 13
7.7 Interim Analysis: 13
7.8 Data Monitoring Committee (DMC): 14
7.9 Changes From Protocol 14
8. Transfer of documentation, data and reporting 14
9. List of Tables, Figures and Listings 17

Abbreviations

AD	Atopic dermatitis
ANCOVA	Analysis of Covariance
EASI	Eczema Area and Severity Index
FAS	Full Analysis Set
FTIR	Fourier Transform Infrared
ISGA	Investigators Static Global Assessment
NMF	Natural moisturizing factor
OCT	Optical Coherence Tomography
PPS	Per protocol set
PS-OCT	Polarization sensitive OCT
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCS	Topical corticosteroid
TEWL	Trans-Epidermal Water Loss

1. Introduction:

This study aims to further develop and validate two non-invasive technologies for the assessment of early 'sub-clinical' skin changes associated with TCS adverse effects and to derive an optimum panel of safety biomarkers for use in future clinical trials of topical anti-inflammatory treatments. In addition, this study aims to determine the relative local skin effects (as determined by early biomarkers of local skin changes) rather than clinical efficacy of crisaborole (2%) ointment compared to a potent TCS in participants with AD.

2. Study Methods

2.1 Study Design

This is an observer-blind, randomized within-subject controlled clinical trial. The participants will apply treatment on designated treatment areas (void of signs of AD) on their front volar forearm for 4 weeks, there will be a further 4 weeks in the study without treatment. Subjects will attend the study centre each working day of week 1 to allow for compliance monitoring including application supervision, product weighing and diary review.

Participants will attend 8 clinic visits during the study:

- Visit 1 (screening) will be performed at baseline (day 1)
- Visit 2 will be performed after 1 day of treatment
- Visit 3 will be performed after 2 days of treatment
- Visit 4 will be performed after 3 days of treatment
- Visit 5 will be performed after 4 days of treatment
- Visit 6 will be performed after 14 days of treatment (day 15)
- Visit 7 will be performed after 28 days of treatment (day 29)
- Visit 8 will be performed after 28 days of treatment and 28 days of washout (day 57)

There will be two treatments applied:

crisaborole (2%) ointment
betamethasone valerate (0.1%) cream

The primary objective is superiority: that crisaborole use will result in less epidermal thinning than the equivalent regimen with betamethasone valerate. The secondary objectives are: investigating the difference between the two treatments on tolerability, skin barrier function, dryness and natural moisturising factor and the ability to detect sub-clinical changes associated with adverse effects.

It is planned to recruit 37 adults (male and female, aged 18-65) with personal history of atopic dermatitis but no current eczema on the volar forearms and no possible allergy to the ingredients in the study medications (allowing for a 10% drop-out rate to meet the target of

33 subjects). They will not be permitted to use topical product on the test area for 7 days prior to baseline or to use a tanning bed for 28 days prior to baseline.

Subjects will remain in the study for 8-9 weeks.

At each study visit, concomitant medication and any AEs are noted in the Case Report Form (CRF). The study medication will be collected and weighed in order to estimate cream consumption.

Assessors will be blind to the treatment assigned to each site. Due the difference in consistencies between the two treatments (cream or ointment) subjects will not be blinded to the treatment assigned to each study site.

2.2 Randomisation

Screening will take place either before or at the same visit as day 1. Those eligible to take part will be randomised on day 1 with each subject testing both treatments – one on each of the left or right lower volar forearm. The randomisation list will be provided by the SSU and the SSU will unblind the database after database lock. The interim analysis has been designed to be done on blinded data.

The pharmacy and a statistician (independent of the study statistician) will have access to the randomisation master list. Since only the research team assessing the study endpoints are blind to the treatment allocation and participants are all prescribed both treatments, no emergency unblinding arrangements are necessary.

2.3 Sample size:

The primary statistical analyses will compare the change in epidermal thickness from baseline to 28 days between treatments: betamethasone valerate cream vs crisaborole, utilising the within participant comparisons of left vs right forearm. Assuming that the change from baseline at day 28 in the betamethasone valerate group will be approximately -4.44μm and a standard deviation of 5 μm (for the change from baseline within each participant), to detect a reduction in this change of 80% to -0.88 μm in the crisaborole arm with 80% power, a parallel group study (one group for betamethasone valerate and one group for crisaborole) would require 33 participants in each group.

The study described here is comparing within participants (left vs right arm) rather than a parallel group (between participants) design, however it is assumed that this within patient comparison will have greater power than the parallel group design. This assumption is necessary because no information is available in the literature as to the standard deviation of the difference between change from baseline on the TCS arm and change from baseline on the crisaborole arm. Assuming that the correlation between these two 'change from baseline' measures will be greater than zero then the within participant comparisons can be assumed to have greater power than a parallel group design.

2.4 Timelines

Planned milestones are as follows;

First subject in: December 2020
Interim analysis: After 15th subject complete* (est. May 2021)
Last subject complete: est. 30 September 2021
Full database delivered to SSU: (est. 30 October 2021)
Blind data review: SSU create tables: 6-8 weeks
Team review blind outputs
Data Base lock
Statistical analysis: 6-8 weeks after database lock
Statistical report: containing TFLs and brief text

*Interim analysis to take place once 15 participants have had their final assessment at day 57.

Final analysis will take place once all participants have had their final assessment at day 57 or have discontinued and the data has been fully cleaned and the database locked.

Completion of the SAP, data cleaning and a blind review will take place prior to data base lock. During blind review all decisions about protocol deviations (ITT and PP populations) and analyses (such as assumptions checking) will be made. Once all these activities have taken place then the database will be locked and unblinded.

3. Data Collection:

Data is to be collected in a custom electronic data capture system designed by the Clinical Trials Research Unit (CTRU) within the University of Sheffield. Adverse events will be coded to MedDRA preferred terms & system organ class within the database. Data will be provided to the SSU as clean csv files.

Data transfers between the study team and Pfizer will be in csv format, final data transfers (after final analysis) from the SSU to Pfzier will be in pre-agreed SAS format. For further details of the transfer of documentation, data and reporting between the study team, the SSU and Pfizer see section 8.

4. Analysis Objectives:

4.1 Primary objective:

To determine whether twice daily treatment with crisaborole (2%) ointment, compared to betamethasone valerate (0.1%) cream, for up to 4 weeks is a cause of skin atrophy in patients with atopic dermatitis.

4.2 Secondary objective:

To determine whether there is a difference between crisaborole (2%) ointment and betamethasone valerate (0.1%) cream on:

- Kinetics of changes in epidermal thickness
- Tolerability
- Skin barrier function
- Skin dryness
- Levels of natural moisturising factor

4.3 Exploratory objectives:

To investigate whether OCT-derived biomarkers (other than the established structural OCT biomarker) enable the accurate quantification of tissue changes (vascular and matrix) associated with epidermal atrophy in response to TCS treatment. Biomarker measurements from the images will include:

- Superficial plexus depth (μm) from angiographic OCT images
- Mean vessel diameter (μm) from angiographic OCT images
- Vessel density (segments/mm^2) from angiographic OCT images
- Collagen matrix index from polarisation sensitive OCT images

To investigate whether FTIR spectroscopy-derived biomarkers enable the accurate quantification of skin barrier condition and function in response to TCS treatment. Biomarker measurements from the spectra will include:

- NMF levels in the skin
- Lipid Structure

To investigate the number of participants with FLG loss-of-function mutations and explore if there is any evidence of a relationship to treatment effects.

To identify (by completing the objectives above) a panel of biomarkers that best characterises epidermal atrophy.

5. Analysis Sets and Protocol Deviations

Full Analysis Set (FAS): All subjects who were randomised into the study.

Per-protocol set (PPS): All participants who are deemed to have no major protocol violations that could interfere with the objectives of this study. This is a sub-population of the FAS.

Safety set: All randomised participants who receive at least 1 dose of test or reference cream.

All efficacy analyses and summaries will be performed on the FAS. If there are concerns about protocol deviations at the blind review, then a sensitivity analysis of the primary objective may be performed on the PPS.

Safety summaries will be performed on the safety set.

Prior to unblinding, a blind review of the data will be performed. The objective of the review is to identify protocol deviations and data queries and to make decisions regarding data analytical issues under blind conditions. Important violations of eligibility criteria and other deviations from the protocol will be assessed in cooperation with the study team. Important deviations from the protocol may lead to exclusion of a participant from the PPS. All deviations will be discussed and agreed prior to the unblinding of the data.

6. Endpoints and Covariates

6.1 Primary endpoints

- Change in Epidermal thickness measured by structural OCT (day 29 - day 1)

6.2 Secondary endpoints

- Epidermal thickness measured by structural OCT during and after 28 days treatment:
  - Change in epidermal thickness (day 15 - day 1)
  - Change in epidermal thickness (day 57 - day 29)
- Erythema (visual redness) score during and after 28 days treatment:
  - Erythema score change from baseline (day 15, day 29, day 57)
- Objective redness as assessed with a Mexameter during and after 28 days treatment
  - Objective redness change from baseline (day 15, day 29 and day 57)
- Trans-Epidermal Water Loss during and after 28 days treatment
  - TEWL change from baseline (day 15, day 29, day 57)
- Skin barrier integrity after 28 days treatment:
  - Difference in $TEWL_{ts20}$ between the two treatments (day 29)
- Visual skin dryness during and after 28 days treatment:
  - Dryness change from baseline (day 15, day 29, day 57)
- NMF at the end of treatment (quantified from superficial stratum corneum samples):
  - Difference between the two treatments (day 29)

6.3 Exploratory endpoints:

Angiographic OCT endpoints

- Superficial plexus depth (µm)
  - Change from baseline/day 1 in superficial plexus measurement (day 15, day 29, day 57)
- Mean blood vessel diameter (µm)
  - Change from baseline/day 1 in mean blood vessel diameter (day 15, day 29, day 57)
- Blood vessel density(segments/mm^2)
  - Change from baseline/day 1 in blood vessel density (day 15, day 29, day 57)

Polarisation sensitive OCT image (PS OCT) endpoints

- Collagen matrix index
  - Change from baseline/day 1 in collagen matrix index (day 29)

FTIR spectroscopy endpoints

- Carboxylate levels
  - Change from baseline/day 1 in carboxylate levels (day 15, day 29, day 57)
- Stratum corneum lipid structure (FTIR and tape stripping)
  - Difference between groups in stratum corneum lipid structure (day 29)
- Number if FLG loss-of-function mutation carriers
  - Count result from saliva sample (day 1)
- Descriptive statistics split by FLG mutation grouping
  of TEWL split by mutation grouping (day 1, day 15, day 29, day 57)
  - TEWL (day 1, day 15, day 29, day 57)
  - Epidermal thickness (day 1, day 15, day 29, day 57)

6.4 Variables

Epidermal Thickness

Triplicate measurements will be performed at each test site (upper part of the right and left volar at baseline (day 1), after 2 weeks treatment (day 15), after 4 weeks treatment (day 29) and 4 weeks after treatment cessation (day 57) using Structural OCT image capture at depth of focus 1.0mm and optical resolution of 7.5x5.0 µm. The average (mean) reading for each patient at each time point at each site will be used in the analysis.

TEWL

Duplicate measurements will be performed at each test site (upper part of the right and left lower volar forearm and lower part of the right and left lower volar forearm) at baseline (day 1), after 2 weeks treatment (day 15), after 4 weeks treatment (day 29) and 4 weeks after treatment cessation (day 57) using an AquaFlux condensing chamber probe. A fourth measurement may be taken if the technician feels that one of the previous readings was abnormal. The average reading for each patient at each time point at each site will be used in the analysis.

On the lower part of the right and left volar forearms, an alternative measurement of TEWL after tape-stripping will be done after 4 weeks treatment (day 29). This outcome is known as $TEWL_{ts20}$.

Redness

Visual scoring of the redness (erythema) of the subject's skin by an expert will take place at baseline (day 1), after 2 weeks treatment (day 15), after 4 weeks treatment (day 29) and 4 weeks after treatment cessation (day 57). Scores will be on a scale from 0 to 3 and will be graded by two observers independently. The upper and lower volar forearms on each side will be combined to give one overall result for the right and one overall result for the left.

Objective scoring of the sites will also be measured using a mexameter. Four repeats per site will be made; the average reading for each patient at each time point at each site (upper part of the right and left lower volar forearm and lower part of the right and left lower volar forearm) will be used in the analysis. A fourth measurement may be taken if the technician feels that one of the previous readings was abnormal.

Dryness

Visual scoring of the dryness of the subject's skin by an expert will take place at baseline (day 1), after 2 weeks treatment (day 15), after 4 weeks treatment (day 29) and 4 weeks after treatment cessation (day 57). Scores will be on a scale from 0 to 4 and will be graded by two observers independently. The upper and lower volar forearms on each side will be combined to give one overall result for the right and one overall result for the left.

NMF levels

Samples for analysis of stratum corneum NMF levels will be collected by tape stripping after 4 weeks of treatment (single time point, day 29). One sample will be collected from each sampling site (tape-strips/discs 1-3 on lower right and left volar forearm). The samples will be analysed separately.

Product Consumption

Product consumption will be based on the difference in weight of the ointment and cream between the start (day 1) and end (day 29) of treatment phase.

Adverse Events

Participants will record AEs throughout the study in their diaries with the information transferred to the CRF at day 29 and day 57.

FLG loss-of-function mutations

Saliva samples will be collected at baseline (day 1) to obtain genomic DNA for determination of participant FLG gene status. Samples will undergo DNA extraction and genotyping at the

University of Sheffield for the 5 common European loss-of-function FLG mutations that have been reported to confer increased AD risk.

7. Statistical Analyses

The primary and secondary analyses will identify where there is evidence of a difference between the two treatments in the change from baseline and which biomarkers are able to identify this difference in the clinical trial setting. Exploratory analyses will investigate whether a subset of the OCT endpoints can be used to non-invasively identify skin changes.

Outcome and demographic data will be summarised at each time point using appropriate descriptive statistics such as N, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

7.1 Primary Analysis

The primary analysis of change in epidermal thickness over 28 days treatment will be estimated using a repeated measures mixed model with change from day 1 as the outcome, treatment, timepoint as factors together with a treatment by timepoint interaction, subject as a random effect and baseline as a covariate. The estimate of change from baseline to day 29 from this model will be the primary outcome, the estimate of change from day 1 to day 15 and change from day 29 to 57 will be secondary as described by in section 7.2.

7.2 Secondary Analysis

The analysis of three of the secondary endpoints will use a repeated measures mixed model with change from day 1 (to day 15, day 29, day 57) as the outcome, treatment, timepoint as factors together with a treatment by timepoint interaction, subject as a random effect and baseline as a covariate.
The model will be used to estimate the difference between treatment arms for the change from baseline to day 29.

If there is a significant difference observed in the change from baseline to day 29, then the change from day 1 to day 15, and the change from day 29 to day 57 will also be assessed. If there is no statistically significant difference in the change from baseline to day 29 then we will not test further timepoints.

Summary statistics will be presented for all timepoints.

This applies to:

- Change in epidermal thickness (change from day 1 to day 15, and from day 29 to day 57 as secondary endpoints)
- Change in redness/erythema
- Change in Trans-Epidermal Water Loss (TEWL)
- Change in visual skin dryness

The Change in $TEWL_{ts20}$ after 28 days treatment will use an ANCOVA model with change from day 1 to day 29 as outcome, treatment as a factor, subject as a random effect and baseline as a covariate. The analysis of Natural Moisturising Factor after 28 days treatment (day 29) will

use a paired analysis (such as a t-test, depending on the distribution of the data) unless it is necessary to adjust for any covariates, in which case an ANCOVA will be used.
If any of the above models do not fit satisfactorily or appear to be over fitted the analysis may be changed to look at change from baseline to day 29 and change from day 29 to 57 separately.

Since these analyses are exploratory, no adjustment for multiplicity will be made.

7.3 Exploratory Analysis

Discriminant analysis will be used to determine which of the new biomarkers provide the most informative and sensitive data pertaining to the atrophic changes induced by TCS treatment. This will be accomplished by assessing the ability of each biomarker to differentiate the skin of participants before and after treatment with the potent TCS, which is known to induce sub-clinical atrophic skin changes within the treatment window.

The endpoints that will be explored this way will be:

- Superficial plexus depth (μm) (day 1, day 15, day 29, day 57)
- Mean blood vessel diameter (μm) (day 1, day 15, day 29, day 57)
- Blood vessel density (day 1, day 15, day 29, day 57)
- Collagen matrix index (day 1, day 15, day 29, day 57)
- Carboxylate levels (day 1, day 15, day 29, day 57)
- Stratum corneum lipid structure (day 29)

Furthermore, summaries of the key outcomes (TEWL and epidermal thickness) by visit (day 1, day 15, day 29) will be made split by FLG loss-of-function mutation carriers.

Exposure and Compliance
A summary of the number of treatment days and the used weight per treatment day by treatment willl be provided.

7.4 Adverse event data:

All Adverse Events will be summarized for all subjects enrolled in the study – both the number of participants with an AE and the total number of AEs. AEs will be tabulation by system organ class and by preferred term, as well as severity and relationship to treatment. Finally, those AEs which are specifically recorded as related to one of the test sites, the AEs will be summarised by test site. A listing, by participant number, will be produced to show the AEs at the worst severity and worst relationship to treatment.

7.5 Multiplicity considerations

All analyses in this SAP will be carried out with a two sided 5% significance level.

Secondary analyses are considered to be exploratory and so no adjustment will be made for multiplicity.

7.6 Missing and unusual data

Missing data will not be replaced. If appropriate the drop out rate will be calculated and analysed.

During data review (prior to data base lock and unblinding), readings that are incorrect, i.e. outside the equipment measurement range, will be removed. However, all readings that are possible, even if they are unusually low or high, will be kept in the analysis.

7.7 Interim Analysis:

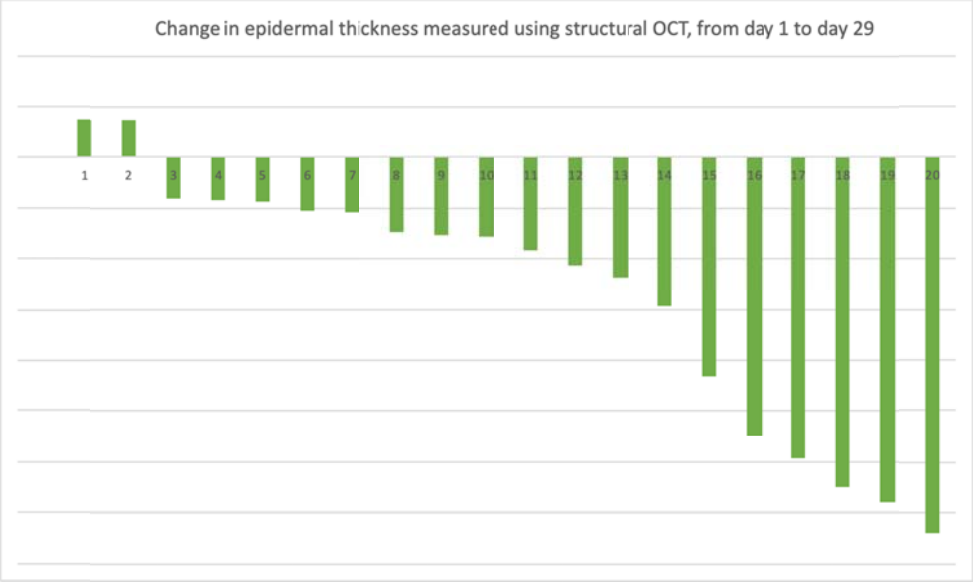
It is of interest to review the data at an interim point to assess the ability of key biomarkers (epidermal thickness and Carboxylate levels) to detect any thinning of the skin over the first 4 weeks of the study. In order to explore this data without breaking the blind or introducing unplanned statistical analysis the following graphical approach is proposed:

For each patient with complete data, the change from baseline to day 29 will be calculated (for left and right arms separately). All the available data will be displayed together and no attempt will be made to identify which observations are related to each treatment. For each endpoint of interest the observations will be ordered according to size and plotted (see example below). This plot will allow clinical interpretation of the raw data to give an early indication of the magnitude of change in skin thickness that is being observed and the variation in that change.

A similar plot of the change from day 29 to day 57, with the observations ordered in the same way, will allow an early look at the recovery of the skin once treatment ends.

A further analogous plot showing skin barrier integrity (TEWLts20) after 28 days treatment will also be created.

Each bar in the plot represents the observation from a single arm, thus each patient will contribute two bars but these will not be linked in the plot.



7.8 Data Monitoring Committee (DMC):

No DMCs are planned for this trial.

7.9 Changes From Protocol

The interim analysis described in section 7.7 was not included in the protocol.

8. Transfer of documentation, data and reporting

Data, documentation and reporting will be shared between the Study team, CTRU, SSU and Pfizer as detailed below. The transfers will use a mutually agreeable electronic transmission method that is demonstrated to be compatible with uploading to the targeted Pfizer database or Pfizer systems and that protects the security and integrity of the data. All deliverables provided to Pfizer will be written in English.

Documentation

- Monthly status reports will be provided to Pfizer by **the study team** in Excel Format, SAS Format, or XPT Format to include:
    - monthly updates of first participant first visit, participant screened, and randomized to date, screen failures to date
    - Participants completed; and
    - any other information as may reasonably be requested by Pfizer
- At the time of study reporting **the SSU** will provide listings (pdf document) by Study subject, for all enrolled Study subjects (not including screen failures) for the following variables as a minimum:
    - subject no.,
    - enrollment date,
    - randomization date,
    - dosing date
- The **study team** will provide the follow documents to Pfizer and the SSU in the form of one or more Portable Document Format ("**PDF**") files and as they become available:
    - annotated CRFs
    - an electronic "Data Dictionary" consisting of all versions of the CRFs used in the Study, annotated with variable names and corresponding datasets
    - documentation of dictionary coding versions used to code medications and SAEs/AEs
    - Any derivations used at the point of data entry or during data cleaning
    - TMF-associated documentation, including, but not limited to:
        - , blank/template CRF,
        - CRF approval(s),
        - clinical data change report,
        - all versions of CRF completion guidelines,
        - completed CRFs,
        - database entry and database user acceptance testing documentation,
        - data management plan(s) (inclusive of edit checks),

  - data review plan(s) and database release documentation,
  - any other documentation as may reasonably be requested by Pfizer

- The **SSU** will provide SAP for review and at sign off (plus if any amendments are required)
  - Any derivations used for the analysis will be included in the SAP/added to an appendix of the SAP as appropriate
  - relevant statistical analysis assumptions or plans will be included in the SAP/added to an appendix of the SAP as appropriate

Clinical Datasets

A "**Clinical Dataset**" consists of all Study Data (with certain personal identifiers removed) available to Trust at the time of transfer. Clinical Datasets may include raw datasets and/or analysis datasets. Trust will transfer Clinical Datasets and in the form of SAS Export/Transport file format (XPT) files or CSV files as detailed below.

Test transfers

Prior to transfer of a given Clinical Dataset to Pfizer, **the study team** will transfer test data to support the effective transfer of such Clinical Dataset. A test data set will consist of complete "dummy" data for at least 5 hypothetical or actual Study subjects. Pfizer will perform certain checks on test data to determine if the transmission meets Pfizer requirements in content and process and if the data will load successfully into the target Pfizer database. Trust will work with Pfizer if changes are needed in the data formatting or transmission process to ensure data quality and usability. Trust will transfer additional sets of test data if needed after such changes are made, as well as if there are any changes in the Study variables or data collection tools during the Study. **Transfers from the study team will be of RAW data in csv format.**

When a test transfer is available it will be provided to the SSU by the **study team**.

Data transfers

The study team will transfer a Clinical Dataset to Pfizer: after fifteen (15) of subjects dosed and after study completion.

At the time of study reporting (when the final analysis is complete) the **SSU** will provide clinical datasets in SAS format. A test transfer can be done in advance, however, there may be small changes to variables up until the final analysis is agreed.

Data cleaning and validation

Pfizer, the **study team** and **the SSU** will alert each other promptly if they discover that any data within a Clinical Dataset fails to meet appropriate quality standards. This may include data queries from **Pfizer** or the **SSU** that **the study team** will investigate and resolve.

Results Summary

The **SSU** will provide tables and listings to the **study team** and **Pfizer** following the final analysis, the format of these will be agreed in advance and will include:

- subject population summaries
- efficacy results
- safety results
- the SSU will advise on statistical interpretation of primary results

In addition, the study team may provide commentary on the objectives and study design and clinical interpretation.
Timelines for the delivery of the tables and listings will be agreed between the study team, the SSU and Pfizer.

Study Report

- Whilst the **SSU** will input and advise with respect to the statistical design, methodology and interpretation the **study team** will be responsible for writing the study report.
- A draft of the written Study Report will be delivered to Pfizer in accordance with the information and formatting as agreed to by **the study team** and in accordance with ICH-E3 guidelines. The Study Report will reflect the results of the Study as a whole. **Study team** will provide Pfizer with an opportunity to review and comment on the draft Study Report for at least thirty (30) days after Pfizer's receipt of the draft Study Report, and Trust and Principal Investigator will consider in good faith any comments reasonably
- Within five (5) months after the last subject's last visit or database lock or upon early termination of the study, whichever occurs first, **the study team** will provide Pfizer with the final Study Report. In case of early termination of the study (before Study Completion), the Study Report will include, at minimum, the Study Results through the date of termination. Unless otherwise agreed in writing, The Trust may submit the Study Report to applicable regulatory authorities.
- Unless otherwise agreed by Pfizer, the Study Report will address:
    - Ethics
    - Investigators and Study administration
    - Study objectives
    - investigational plan
    - Study subjects
    - efficacy evaluation
    - Drug compliance/adherence evaluation
    - safety evaluation
    - discussion and overall conclusions; supportive tables, figures and graphs;
    - biomarker findings; and
    - any other information as may reasonably be requested by Pfizer.

9. List of Tables, Figures and Listings

Tables

14.1.1	Disposition (Full Analysis Set)
14.1.2	Important PDs (Full Analysis Set)
14.1.3	Patients excluded from analysis populations (Full Analysis Set)
14.1.4	Demographic data (Full Analysis Set)
14.1.5	Baseline eczema history (Full Analysis Set)
14.1.6	Medical History (Full Analysis Set)
14.1.7	Temperature and humidity during skin assessments (Full Analysis Set)
14.2.1	Epidermal thickness. (Full Analysis Set)
14.2.1.1	Change in epidermal thickness during and after 4 weeks of treatment (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.1.2	Analysis of epidermal thickness change (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set) *Note for this table and similar tables for the secondary endpoints – only those comparisons carried out will be included – see section 7.2*
14.2.2	TEWL (g/m2h) (Full Analysis Set)
14.2.2.1	Change in TEWL (g/m2h) during and after 4 weeks of treatment (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.2.2	Analysis of change in TEWL (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.3	$TEWL_{ts20}$ (g/m2h) (Full Analysis Set)
14.2.3.1	Change in $TEWL_{ts20}$ (g/m2h) after 4 weeks of treatment (day 29) (Full Analysis Set)
14.2.3.2	Analysis of change in $TEWL_{ts20}$ following 4 weeks of treatment(Full Analysis Set)
14.2.4	NMF (Full Analysis Set)
14.2.4.1	Analysis of NMF (day 29) (Full Analysis Set)
14.2.5	Investigator visual scores for redness (Full Analysis Set)
14.2.5.1	Change in visual score for redness during and after 4 weeks of treatment (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.5.2	Analysis of change in visual score for redness (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.6	Objective Redness (Mexameter) (Full Analysis Set)
14.2.6.1	Change in Objective Redness (Mexameter) during and after 4 weeks of treatment (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.6.2	Analysis of change in Objective Redness (Mexamater) (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.7	Dryness(Full Analysis Set)
14.2.7.1	Change in Dryness during and after 4 weeks of treatment (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.7.2	Analysis of change in dryness (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.8	Superficial plexus depth (μm) (Full Analysis Set)
14.2.8.1	Change from baseline in superficial plexus depth (μm) (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.9	Mean blood vessel diameter (μm) (Full Analysis Set)
14.2.9.1	Change from baseline in mean blood vessel diameter (μm) (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)

14.2.10	Blood vessel density (segments/m^2) (Full Analysis Set)
14.2.10.1	Change from baseline in blood vessel density (segments/m^2) (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.11	Collagen matrix index (Full Analysis Set)
14.2.11.1	Change from baseline in collagen matrix index (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.12	Carboxylate levels (FTIR) (Full Analysis Set)
14.2.12.1	Change from baseline in carboxylate levels (FTIR – indirect NMF) (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.13	Stratum corneum lipid (Full Analysis Set)
14.2.13.1	Change from baseline in stratum corneum lipid (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
14.2.14	Summary of FLG (Full Analysis Set)
14.2.14.1	Summary of epidermal thickness by mutation status(Full Analysis Set)
14.2.14.1.1	Analysis of change in epidermal thickness (day 29 – day 1) within mutation status (Full Analysis Set)
14.2.14.2	Summary of TEWL (g/m2h) by mutation status(Full Analysis Set)
14.2.14.2.1	Analysis of change in TEWL (g/m2h) (day 15 – day 1, day 29 – day 1, day 57 – day 1) within mutation status (Full Analysis Set)
14.2.15	Total Product consumption (Safety Analysis Set)
14.3.1	Number of patients experiencing AEs (Safety Analysis Set)
14.3.2	Adverse Events by system organ class and preferred term (Safety Analysis Set)
14.3.x	Adverse Events - further tables as appropriate (Safety Analysis Set)
BDR1.1	Summary of epidermal thickness by location (Full Analysis Set)
BDR1.2	Summary of epidermal thickness change by location (day 29 – day 1) (Full Analysis Set)
BDR1.3	Summary of epidermal thickness change after treatment cessation by location (day 57 – day 29) (Full Analysis Set)
BDR2.1	Summary of TEWL (g/m2h) by location (Full Analysis Set)
BDR2.2	Summary of TEWL (g/m2h) change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR3.1	Summary of $TEWL_{ts20}$ (g/m2h) by location (Full Analysis Set)
BDR3.2	Summary of $TEWL_{ts20}$ (g/m2h) change by location (day 29 – day 1)
BDR4.1	Summary of NMF by location (Full Analysis Set)
BDR4.2	Summary of NMF change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR5.1	Summary of visual scores for redness (erythema) by location (Full Analysis Set)
BDR5.2	Summary of visual scores for redness (erythema) change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR6.1	Summary of Objective redness (Mexameter) by location (Full Analysis Set)
BDR6.2	Summary of Objective redness (Mexameter) change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR7.1	Summary of Dryness by location (Full Analysis Set)
BDR7.2	Summary of Dryness change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR8.1	Summary of Superficial plexus depth (µm) by location(Full Analysis Set)
BDR8.2	Summary of Superficial plexus depth (µm) change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR9.1	Summary of Mean blood vessel diameter (µm) by location (Full Analysis Set)

BDR9.2	Summary of Mean blood vessel diameter (μm) change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR10.1	Summary of blood vessel density (segments/m^2) by location (Full Analysis Set)
BDR10.2	Summary of blood vessel density (segments/m^2) change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR11.1	Summary of collagen matrix index by location (Full Analysis Set)
BDR11.2	Summary of collagen matrix index change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR12.1	Summary of carboxylate levels (FTIR) by location (Full Analysis Set)
BDR12.2	Summary of carboxylate levels (FTIR) change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)
BDR13.1	Summary of stratum corneum lipid by location (Full Analysis Set)
BDR13.2	Summary of stratum corneum lipid change by location (day 15 – day 1, day 29 – day 1, day 57 – day 1) (Full Analysis Set)

Listings

16.2.1	Discontinued patients (All patients)
16.2.2	Protocol deviations (Full Analysis Set)
16.2.3	Patients excluded from analysis populations (All patients)
16.2.4.1	Demographic data (Full Analysis Set)
16.2.4.2	Baseline eczema history (Full Analysis Set)
16.2.4.3	Medical history (Full Analysis Set)
16.2.4.4	Patient routine (Full Analysis Set)
16.2.5	Cream consumption (Full Analysis Set)
16.2.6.1	Epidermal thickness (Full Analysis Set)
16.2.6.2	TEWL (Full Analysis Set)
16.2.6.3	Investigator visual scores for redness (Full Analysis Set)
16.2.6.4	Objective erythema (Full Analysis Set)
16.2.6.5	Objective Redness (Mexameter) (Full Analysis Set)
16.2.6.6	$TEWL_{ts20}$ (Full Analysis Set)
16.2.6.7	Skin surface dryness (3D skin images) (day 29 – day 1) (Full Analysis Set)
16.2.6.8	Superficial plexus depth (Full Analysis Set)
16.2.6.9	Blood vessel diameter (Full Analysis Set)
16.2.6.10	Blood vessel density (Full Analysis Set)
16.2.6.11	Collagen matrix index (Full Analysis Set)
16.2.6.12	Carboxylate levels (Full Analysis Set)
16.2.6.13	Stratum corneum lipid (Full Analysis Set)
16.2.6.14	$TEWL_{ts5}$ (Full Analysis Set)
16.2.6.14	$TEWL_{ts10}$ (Full Analysis Set)
16.2.6.14	$TEWL_{ts15}$ (Full Analysis Set)
16.2.6.15	Patient tolerability scores (VAS) (Full Analysis Set)
16.2.6.16	Total Cream consumption (Full Analysis Set)
16.2.6.17	NMF (Full Analysis Set)
16.2.6.18	FLG (Full Analysis Set)
16.2.7	AEs (Safety Analysis Set)

Figures:

Figure 14.2.1.1 Epidermal thickness by visit (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.2.1 Erythema (visual redness) by visit (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.3.1 Objective redness (mexameter) (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.4.1 TEWL (g.m2h) by visit (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.7.1 Skin surface dryness (µm) (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.8.1 NMF levels at day 29(Full Analysis Set)
Figure 14.2.9.1 Superficial plexus depth (µm) (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.10.1 Mean blood vessel diameter (µm) (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.11.1 Blood vessel density (segments/mm^2) (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.12.1 Collagen matrix index (day 1, day 29) (Full Analysis Set)
Figure 14.2.13.1 Carboxylate levels (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.14.1 Stratum corneum lipid structure (day 29) (Full Analysis Set)
Figure 14.2.15.1 Epidermal thickness split by FLG mutation (day 1, day 15, day 29, day 57) (Full Analysis Set)
Figure 14.2.16.1 TEWL split by FLG mutation (day 1, day 15, day 29, day 57) (Full Analysis Set)