Statistical Analysis Plan Update

EXP-1223

Explorative trial evaluating the efficacy, tolerability and safety of LEO 43204 applied in a split-face (left/right) topical design in adults with moderate to severe acne

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1 Abbreviations and definition of Terms

Abbreviations	Meaning of abbreviations in document
ADaM	Analysis Data Model (The data set structure used for analysis data sets when following the CDISC consortium)
ADRG	Analysis Data Reviewer's Guide
CDISC	Clinical Data Interchange Standards Consortium
FAS	Full-Analysis Set
IMP	Investigational Medicinal Product
LOCF	Last Observation Carried Forward
OC	Observed Cases
PP	Per-Protocol
SAP	Statistical Analysis Plan
SAPU	Statistical Analysis Plan Update
SAS	Safety Analysis Set
SDTM	Standard Data Tabulation Model (The data set structure used for the base data sets when following the CDISC consortium)

Terms	Definitions
Randomised	Subject randomised to study treatment
Screened	Subject who enters the screening phase

2 Introduction

This SAPU is based on the Larix template for an ordinary SAP. Since Leo Pharma's standard process is to prepare a SAPU instead of a SAP it was decided to also follow that approach for this study and content which is just repeating information from the protocol will not be included.

This document expands any necessary details on statistical plans in the protocol if such expansion is needed for a complete description. In addition, the document will include all data driven decisions originating from the blind data review prior to un-blinding the study.

The SAPU is based on the protocol version 5.0 of 15 September 2016. The protocol version 5.0 includes all changes implemented in amendments 1 to 4.

3 Analysis Sets

A total of 19 screening failures were seen but not included in the trial.

In accordance with the design in the protocol a total of 40 subjects were enrolled and randomized as

Cohort 1:	3 subjects
Cohort 2:	6 subjects
Cohort 3:	6 subjects
Cohort 4:	25 subjects

3 subjects discontinued before completion:

Subject PPD from cohort 2 was lost to follow up after day 8
Subject PPD from cohort 4 was lost to follow up after week 4
Subject PPD from cohort 4 was lost to follow up after week 8

Subject PPD from cohort 4 withdrew voluntarily after day 3 (after treatment application)
Subject PPD from cohort 4 withdrew voluntarily after day 8
Subject PPD from cohort 4 was lost to follow up after week 4

As planned in the protocol subjects PPD and PPD received 1 and 2 treatment administrations respectively and will not be included the FAS. Other subjects with reduced treatment administration were:

Subject	Number of treatments	Reason
PPD	2	Subject refused 3rd treatment due to local AE (i.e. intolerable response to treatment).
PPD	1	Withdrawal by subject. According to investigator comment subject not interested in continuing participation.

These additional 2 subjects with reduced treatment will, as described in the protocol, be included in the FAS.
The FAS therefore include all 40 randomized subjects except subject PPD and PPD , which gives a total of 38 subjects.

All randomised and exposed subjects will be included in the safety analysis set (SAS). The SAS therefore includes 40 subjects.

A PP analysis set is defined as all subjects who
- complete the trial
- have no other major protocol deviations deemed to influence the evaluation of efficacy

Subjects PPD , PPD and PPD were treated on day 2 and/or 3 although their LSR indicated they should not have been (see further about separate listing on this in the safety section). This was in violation of the protocol, but it is assessed that with respect to efficacy evaluation this is not a problem and the subjects are retained in the PP analysis set. Inspecting actual visit day versus planned visit day subjects PPD and PPD had week 12 visit outside the protocol allowed window of +/- 7 days. The violation was +5 days for subject PPD and +2 days for subject PPD . Other noteworthy deviations are: subject PPD +15 days on week 8 visit, subject PPD +11 days on week 8 visit and subject PPD +12 days on week 4 visit. Although the last three mentioned deviations are relatively large it was decided at the Blind Data Review meeting not to perform visit reallocation or deletion of these data points since this would not necessarily improve the modelling of the recorded data and since it would add extra complication. Overall, the PP analysis set therefore will consist of all subjects in the FAS who completed the trial. The per protocol analysis set thus consists of all subjects except subjects PPD , PPD , PPD , PPD , PPD , PPD , PPD , PPD or a total of 32 subjects.

4   Statistical analyses and presentation of data

4.1   Disposition of subjects

Subject disposition will be presented as described in the protocol.

4.2   Demographics and other Baseline Characteristics

Demographics and baseline characteristics will be presented as described in the protocol. Age will be presented both as a continuous variable and grouped into 18-20, 21-24, and 25-35 years.

4.3   Exposure and treatment compliance

Exposure and treatment compliance will be presented as described in the protocol.

4.3.1   Analysis of primary endpoint

The analysis of the primary endpoint total lesion count at week 12 will follow the description in the protocol. The primary analysis will be based on the FAS analysis set. A sensitivity analysis will include the lateral side of lesion as

a covariate. An additional sensitivity analysis will be performed on the PP analysis set.

Furthermore, if there are missing data then the above analyses will be handled with the below multiple imputation methods and additionally an LOCF and an OC analysis will be included.

Missing data for total lesion count on day 1 or week 12 will be handled using multiple imputation as described in the protocol. The following additional specifications may be given:
- All imputations will be performed by lesion type and treatment group.
- Total lesion will be calculated by suming of inflamed and non-inflamed lesions by simulation

Screening and baseline lession values are very similar. To avoid problems with identifiability in the estimations modeling will only be from baseline and forward.

4.3.2   Secondary Efficacy Analyses

Additional lesion count presentations will be presented as described in the protocol.

Investigator's global assessment will be presented as described in the protocol.

Treatment success derived from IGA will be tabulated and tested by a McNemar's test. This is a minor deviation from the protocol where a Fisher's Exact test is specified. The change in analysis plan stems from the fact that the McNemar's test is designed for paired observations as is the case in this split-face design.

The inflammatory cytokine expression data will be presented as described in the protocol but will due to timing be reported separately from the main CTR.

The analysis of data relating to the microbiome will be specified in a separate analysis plan, and the reporting will be done separately.

The subject's self evaluation of Acne QoL will follow description in the protocol. Item scores will be coded from 0 to 6 with zero most negative and 6 most positive. Four domains are defined by summing item scores as defined in the below table. Missing items will be replaced by the mean of the non-missing data within the same subject, visit and domain. If less than 3 items are scored within a domain the domain sum will be missing.

Self Perception		Role-emotional	
1	Feel unattractive	5	Spending time treating face
3	Feel self-concious	9	Need to have meds or cover-up available
10	Self-confidence affected	8	Meds won't clear face fast enough
2	Feel embarrassed	7	Not looking your best
6	Dissatisfied with self appearance	4	Feel upset
Role-Social		Acne Symptoms	
12	Going out in public	15	Bumps on face
11	Meeting new people	16	Bumps full of pus
14	Interacting with opposite sex (or same sex if gay) a problem	17	Scabbing from acne
13	Socializing with people a problem	18	Concerned with scarring
		19	Oily skin

The subject's self evaluation of TSQM II will follow description in the protocol. Item scores will be coded from 1 to 7 with 1 as the most negative and 7 as the most positive. Four domains are defined by summing item scores as defined in the below table. The domain scores will be scaled from 0 to 100, with 0 as the lowest possible score and 100 as the highest possible score. For domains with 3 items one item may be missing and then the domain score is based on the two non-missing items. For domains with two items both of these must be present for a domain score to be calculated.

Effectiveness		Side effects	
1	How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?	4	How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?
2	How satisfied or dissatisfied are you with the way the medication relieves symptoms?	5	How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?
		6	How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?
Convenience		Global satisfaction	
7	How satisfied or dissatisfied are you with how easy the medication is to use?	10	How satisfied are you that the good things about this medication outweigh the bad things?
8	How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?	11	Taking all things into account, how satisfied or dissatisfied are you with this medication?
9	How satisfied or dissatisfied are you by how often you are expected to use/take the medication?		

The subject's global cosmetic score will be presented as described in the protocol. The following transformation from the eCRF categories to numerical ratings will be used:

Category	Rating
Much worsened	0
Somewhat worsened	1
No change	2
Somewhat improved	3
Much improved	4

4.4 Safety

Safety parameters will be evaluated for the safety analysis data set.

4.4.1   Adverse Events

The treatment emergent adverse events will be tabulated in the following categories:

- Cutaneous
    - Outside of treatment area
    - Leo 43204 Gel 0.018%
    - Vehicle
- Non-cutaneous

The split between cutaneous and non-cutaneous will be based on the MedDRA preferred term text as follows:

- Cutaneous
    - Application site plain
    - Application site pruritus
- Non-cutaneous

- o   Headache

- o   Nausea

Frequencies, incidences and incidence rates for treatment emergent adverse events will be presented in the following tables

- Overall summary table of adverse events

- Adverse events presented by system organ class and preferred term

- Adverse events presented by system organ class and preferred term and severity

- Related adverse events presented by system organ class and preferred term

All adverse events will be listed split by treatment emergent and non-treatment emergent. Adverse events leading to withdrawal or discontinuation of treatment will be listed.

A listing of unacceptable LSR events, following section 11.3.10 in the protocol, and LSR scores for not administering the 2nd or 3rd treatment (table 1 in protocol) will be shown together with reason for no treatment.

4.4.2   Other safety endpoints

Vital signs will be presented as described in the protocol.

5 Programming and Quality Control

SDTM data sets are received from the data management provider Novella (formerly TKL). Larix will review the SDTMs and inform Novella and Leo of any deficiencies and discrepancies.

Larix will prepare ADaM data sets, ADRG and define file. ADaM data sets will be QCed by double programming.

Tables, listings and figures will be independently code reviewed by a qualified programmer (statistician for analysis programs) according to Larix SOPs.

ADaM data sets, tables, listings and figures will be produced by SAS ver. 9.4 following Larix' SOPs on programming.

6 Tables, Listings and Figures

The table shells are presented in a separate document.

The following figures will be prepared:

1.   Mean and individual lesion count profiles

2.   Plots of mean and individual profiles of composite LSRs by visit and lateral side

3.   Plots of mean and individual profiles of maximum of right and left side composite LSRs by visit

All data will be listed by subject, visit and treatment (if relevant).

7 Change Log

Edition	Effective on	Reason for revision
1.0	19MAY2017	New version

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