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Statistical Analysis Plan

for Clinical Trial Protocol DS107G-05-AD3

Study Title	A Randomised, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Orally Administered DS107 in Adult Patients with Moderate to Severe Atopic Dermatitis
Study Medication	DS107 Capsules
Type of Study	Multicenter, double-blind, placebo controlled, 2-arm, Phase II study with 16 weeks of active treatment and a 4 week follow up period
Objectives of Study	The primary objective is to compare the efficacy of orally administered DS107 versus placebo, in the treatment of adult patients with moderate to severe Atopic Dermatitis (AD). The secondary objective is to assess the safety of orally administered DS107 versus placebo, in adult patients with moderate to severe AD.
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List of Abbreviations and Definition of Terms

AD	Atopic Dermatitis
AE	Adverse Event
AIS	Athens Insomnia Scale
AMS	***AMS*** Advanced Medical Services GmbH
ATC	Anatomical Therapeutic Chemical
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BSA	Body Surface Area
DGLA	Dihomo-Gamma-Linolenic Acid
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	Electrocardiography
eCRF	electronic Case Report Form
FAS	Full Analysis Set
g	Gram
GLMM	Generalised Linear Mixed Model
ICH	International Conference on Harmonization
IGA	Investigator Global Assessment
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
kg	Kilogram
MAR	Missing at Random
MedDRA	Medical dictionary for Drug Regulatory Affairs
MMRM	Mixed Model with Repeated Measures
NRS	Numeric Rating Scale
No.	Number

POEM	Patient Orientated Eczema Measure
PO-SCORAD	Patient Oriented Scoring of Atopic Dermatitis
PPS	Per-Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCORAD	Scoring of Atopic Dermatitis
SOC	System Organ Class
SOP	Standard Operating Procedure
TMF	Trial Master File
vIGA-AD™	Validated Investigator Global Assessment Scale for Atopic Dermatitis
WHO	World Health Organisation

1 Introduction

This Statistical Analysis Plan (SAP) refers to the Trial Protocol DS107G-05-AD3, final version 5.0 (EU) and version 5.1 (US) dated March 18, 2020 which includes the previously approved versions of the protocol. The SAP will be finalised before any analysis will be conducted. The specifications included in this SAP which have not been mentioned in the study protocol, are restricted to statistical issues, and have no impact on the clinical conduct of the trial.

This SAP describes the analysis to be performed at the end of the trial.

Additions or changes to the analysis planned in this SAP may be defined during the BDRM (Blind Data Review Meeting) and documented in the BDRM protocol which will be approved by the BDRM participants.

The document is written in compliance with the ICH Guidelines E9 and the ***AMS*** SOP ST-02.01 (Statistical Analysis Plan).

1.1 Study Objectives

The primary objective of this clinical trial is to compare the efficacy of orally administered DS107 (2g) versus placebo, in the treatment of adult patients with moderate to severe AD. The secondary objective is to assess the safety of orally administered DS107 (2g) versus placebo, in adult patients with moderate to severe AD.

It is planned to test the trial medication versus placebo in a total of 220 patients.

1.2 General Study Design

This clinical trial will be carried out as a randomised, placebo-controlled, double-blind, parallel group, multi-centre 2-arm Phase 2 study to investigate the efficacy of orally administered DS107 in AD patients.

It is planned that at least 220 patients suffering from moderate to severe AD will be included in this study. All patients will sign an informed consent and undergo screening for study eligibility.

Before the comparative treatment period can commence, patients will return to the site for a baseline assessment of their disease and eligible patients will be randomly allocated to one of the treatment regimens in a 1:1 randomization:

- 2g DS107 (4 DS107 capsules) orally administered once daily for 16 weeks
- Placebo (4 placebo capsules) orally administered once daily for 16 weeks

There is a 4 week follow-up period.

To maintain the double-blind conditions, DS107 capsules and placebo will be identical in appearance.

1.3 Study Population

The study population will consist of male and female patients with confirmed diagnosis of AD aged 18 years or older.

1.4 Study Medication

The following medication supplies will be used in the study:

DS107 capsules:

Each DS107 capsule contains 500mg DGLA as an active ingredient in an opaque, oval soft gelatin capsule.

Placebo capsule:

Each matching placebo capsule contains 500mg of liquid paraffin in an opaque oval soft gelatin capsule.

1.5 Randomisation

Approximately 220 patients will be randomized into double-blind treatment groups in a 1:1 ratio by an IWRS.

- 2g DS107 (4 DS107 capsules) administered once-daily for 16 weeks
- Placebo (4 placebo capsules) orally administered once-daily for 16 weeks

A randomization list permuted by blocks and stratified by site will be generated by the Sponsor or its designee. The randomization schedule with study drug assignments will be generated prior to the start of the study and will be known only to the individuals responsible for labelling the study drug, the statisticians generating the schedule and the IWRS team responsible for implementing the schedule. The IWRS will assign a medication kit number to each patient and the contents will be based on the randomization code.

At the investigational site, each patient will be assigned a patient identifier number during screening that will be used on all patient documentation. The patient identifier number will contain the site number and the patient number assigned in numerical order at the Screening Visit (e.g.: 102-10 for the tenth patient screened at the site number 02). Patient numbers will be assigned in ascending order starting with 01.

The treatment assignment procedure will use blocks of sufficient size to maintain a blind and balance across treatment arms. Following successful completion of the screening/baseline evaluations and confirmation that the patient is eligible for participation, the patient will be randomised to treatment. This will be performed by the Investigator using the IWRS which will assign a medication number to the patient.

1.6 Interim Analysis

An interim analysis may be conducted after at least 50% of planned enrolled patients have completed their Week 16 assessments or an early termination visit. The interim analysis will be conducted in accordance with sponsor standard operating procedure (SOP) “Interim Analysis of Clinical Studies”.

An unblinded interim analysis will be performed by an unblinded independent statistician. Interim data and the results of interim analyses will not be accessible by anyone other than the unblinded statistician. The sponsor will remain blinded with procedures in place to ensure the confidentiality of the interim data, as per the sponsor SOP “Interim Analysis of Clinical Studies”.

The unblinded statistician will make one of the following recommendations to the sponsor based solely upon the primary efficacy endpoints:

- Modify the sample size
- Continue the study as originally planned
- Stop the study due to futility

Further details will be described in an interim statistical analysis plan. No α adjustment will be executed.

Due to the rapidly evolving COVID-19 situation at both a global and country level, a modification to the prospectively planned sample size may be necessary if patient recruitment is not feasible and must be stopped. The interim analysis will safeguard the integrity of the trial and inform whether further patient recruitment is required when conditions at participating sites are amenable to re-initiation of patient recruitment.

1.7 Time Schedule / Study Duration

Patients will come to the clinic on 8 occasions: at Screening/Visit 1, Baseline/Visit 2, Week 4/Visit 4, Week 8/Visit 5, Week 12/Visit 6, Week 16/Visit 7 (end of treatment), Week 18/ Visit 8 (follow up) and Week 20/Visit 9 (follow-up). A telephone visit will also be performed at Week 1/Visit 3.

Patients who discontinue the study early will be asked to attend the investigative site as soon as possible so that assessments scheduled for Visit 7 can be conducted at an Early Termination visit.

In the event that treatment is occurring, a wash out period of up to 4 weeks may be necessary. At the Screening Visit, after giving informed consent to participate, patients will be assessed using the screening examinations. Eligible patients with confirmed AD using the American Academy of Dermatology Consensus Criteria and who meet all the inclusion criteria and do not meet the exclusion criteria at the baseline visit will be enrolled.

During the treatment period and follow-up period patients will be restricted from using any other treatment for AD, with the exception of the same emollients they have been consistently using since the screening visit.

2 Sample Size

In the Phase 2a trial, IGA response rates of 21.6% and 11.8% were observed for DS107 and placebo respectively resulting in a difference in response rates of 9.8%. Due to the prolonged treatment period of 16 weeks, a clinically relevant difference in IGA response rates of 15% was expected for the current study.

Assuming a placebo response rate of 12% and a true response rate difference of 15% at Week 16 and using a two-sided Chi-Square test on a significance of 5%, then 220 evaluable patients (110 patients per treatment arm) will be needed for 80% power to detect this difference as statistically significant. As the following table shows, the number of patients needed for the discovery of a 15% response rate difference depends also on the placebo response rate shown in the left column of the table as decimal numbers:

Number of patients per study group required under the assumptions as follows
Chi-square test, 2 x 2 table, Two Proportions, two-sided.
Sample Size 1 as a function of H1: Proportion 1 and Power.
H1: Proportion 2 - Proportion 1=0,15 Significance Level=0,05 Sample Size 2 / Sample Size 1=1

H1: Proportion 1 = Response Rate Placebo	Power 0,7	0,8	0,9
0,06	63,4	80,3	107,0
0,08	71,2	90,2	120,3
0,10	78,6	99,6	132,8
0,12	85,5	108,4	144,6
0,14	92,0	116,6	155,6
0,16	98,0	124,3	165,9
0,18	103,6	131,4	175,4
0,20	108,8	138,0	184,2

It was assumed that similar estimations apply to the primary endpoint EASI-75.

3 Analysis Populations

The assignment of individual patients to the analysis sets will be determined by the members of the BDRM. The patients will be assigned to the following analysis sets before unblinding:

1. Enrolled Set: The Enrolled Set consists of all patients who sign informed consent.
2. Screen Failures: Screen Failures are patients from the Enrolled Set who do not meet the eligibility requirements and are withdrawn from the study prior to randomisation.
3. Randomised Set: The Randomised Set consists of all patients who are randomised to the study.
4. Safety Analysis Set (SAS): The Safety Analysis Set (SAS) consists of all patients who received at least one dose of the medication. SAS is the analysis population for all safety endpoints. Analysis will be done according to the actual treatment patients received.
5. Full Analysis Set (FAS): The Full Analysis Set (FAS) consists of all patients who were randomised to the study and received at least one dose of study medication. FAS is the primary analysis population for efficacy endpoints. Analysis will be done according to the treatment patients were randomised to.
6. Per-Protocol Set (PPS): The Per Protocol Set (PPS) is the subset of FAS who completed the study without any major violations. Protocol violations will be assessed for each patient in a blinded fashion prior to database lock at a Blind Data Review Meeting (BDRM), and the PPS will also be finalised during this meeting. PPS is a supportive analysis population for efficacy endpoints. Analysis will be done according to the treatment patients were randomised to.

   For PPS the primary endpoint will only be evaluated in an exploratory sense.

4 Data Handling

4.1 General

4.1.1 Data sources

Most of the data collected in connection with this trial are recorded in an eCRF (electronic Case Report Form). The diary data (NRS, AIS, IMP compliance etc) is recorded in the IRT system. All patient data will be entered by the investigator. Details can be found in the data handling manual for this study. The entered data are subjected to plausibility checks. These are detailed in the data validation plan for this study.

4.1.2 Coding

The process of coding is performed according to the ***AMS*** internal Coding SOP and relevant Coding guidelines (e.g. 'MedDRA Points to consider' / 'Best Practices for the use of the WHO Drug Dictionaries').

The data to be coded is extracted into a coding database where the coding is performed. Details of the coding database, the items to be coded, the frequency of coding and the 'MedDRA' version used for coding of diseases and adverse events and the WHO DD version used for coding of medications and the update frequency of the dictionaries are defined in the Coding Specification.

4.1.3 Visits

The analysis visits and points in time will be presented as documented in the database.

4.1.4 Baseline value

The last non-missing value prior to first treatment will be referred to as baseline value and will be used for change from baseline calculations.

4.1.5 Missing values

If only the day is not known completely, for onset dates or start dates missing day information will be assumed as the 1st. If both day and month are missing, the 1st January will be used. For stop dates missing day information will be imputed as the last of the month, if both day and month are missing, the 31st December will be used.

However, if for AEs it is not clear whether the event started prior to or in the treatment period, the onset at day of first treatment will be assumed.

If it is not clear due to a missing or incomplete stop date of a medication whether the medication was taken at least once after the first treatment of the patient, a stop date after the day of the first patient visit will be assumed. The medication will therefore be classified as "concomitant medication". If it is not clear due to a missing or incomplete start date of a medication whether the medication was taken at least once before the first treatment of the patient, a start date before the day of the first patient visit will be assumed. The medication will therefore be classified as "previous medication" (cf. section 4.2.14).

Data from patients who prematurely terminate the trial will be used to the maximum extent possible.

The primary statistical analysis assumes "Missing At Random (MAR)" when handling missing data. The treatment effect obtained under the MAR assumption is essentially that which could have been reached if all patients had fully adhered to treatment or, in other words, the effect a patient may expect if they take the medication as directed. This is sometimes known as the 'de jure' or 'efficacy' estimand. Due to the lack of perfect adherence in practice, the 'de facto' or effectiveness treatment effect will also be estimated. This estimand includes assumptions regarding the treatment effects that could be expected to occur when patients discontinue treatment. The jump to reference method described by Carpenter et al. (2013) will be used to estimate the de facto estimand, using the placebo arm as the reference. This is based on the assumption that patients who discontinue from study drug have no alternative oral treatment option suitable for longer-term use and so their responses are likely to revert to those of the placebo group. An additional sensitivity analysis will evaluate patients who received rescue medication as treatment failures from the visit onwards where rescue treatment started. The sensitivity analyses for missing data will be performed on the FAS only.

4.2 Algorithms for data calculations and modifications

4.2.1 Study Day

The Study Day of an assessment or event will be defined as

Study Day = Date of Assessment - Date of first treatment +1

for assessments performed at/after date of first treatment.

For assessments prior date of first treatment the definition is as follows:

Study Day = Date of Assessment - Date of first treatment

For patients without treatment, study day will not be calculated.

4.2.2 Age

The age of patients at time of consent [in years] is used as documented in the eCRF.

4.2.3 BMI

The Body Mass Index (BMI) of patients at screening is used as documented in the eCRF.

4.2.4 Validated Investigator Global Assessment (vIGA-AD™)

The clinical severity of AD will be evaluated by the Investigator at each visit using the vIGA-AD™ scale.

The vIGA-AD™ scale awards a score of 0-4 based on a 5-point severity scale from clear to severe disease (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease). The scale uses clinical characteristics of erythema, infiltration, papulation and oozing/crusting as scoring guidelines for the overall severity assessment. vIGA-AD™ will be assessed at every clinic visit.

4.2.5 Eczema Area Severity Index (EASI)

EASI quantifies the severity of a patient's AD based on both lesion severity and the percent of BSA affected (Hanifin et al. 2001). The EASI is a composite score ranging from 0-72 that takes

into account the degree of erythema, induration/papulation, excoriation, and lichenification (each scored from 0 to 3 separately, half points are permitted) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.

4.2.6 Pruritus NRS

Severity of pruritus related to AD will be self-assessed by patients daily using the NRS. Patients will be asked to estimate the intensity of pruritus at its worst over the previous 24 hours. The Pruritus NRS is a single-question assessment tool that will be used to assess the patient's worst itch as a result of AD in the previous 24 hours. Patients will score their pruritus due to AD on a scale of 0 – 10, with 0 (no itch) and 10 (worst itch imaginable) (Phan et al. 2012). Patients will complete the rating scale daily starting at screening through to the last study visit.

The baseline NRS is defined as the prorated average of the NRSs reported continuously for 7 days right before and on the baseline visit (i.e. study day -6 to day 1). For post-baseline NRS, the mean weekly worst itch NRS is calculated as the prorated average of the reported daily NRS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3.

4.2.7 Body Surface Area (BSA)

The overall BSA affected by AD will be evaluated (from 0 to 100%) at each visit. One patient's palm represents 1% of his/her total BSA. BSA will be evaluated at every clinic visit.

4.2.8 Dermatology Life Quality Index (DLQI) Questionnaire

The effect of AD on patient quality of life will be self-assessed by the patient at every clinic visit starting from baseline, using the DLQI developed by Finlay and Khan (1994).

DLQI has a maximum value of thirty based on the patients response to ten questions scored according to the following scale:

- Very Much = 3
- A lot = 2
- A little = 1
- Not at all = 0
- Not relevant = 0
- Question unanswered = 0
- Question 7: "prevented work or studying" = 3

4.2.9 Patient Orientated Eczema Measure (POEM)

The POEM will be assessed at each clinic visit, except the screening visit. The POEM developed by Charman et.al. 2004 is a self-assessment of disease severity by the patient. POEM has a maximum value of twenty eight based on the patient's response to seven questions scored according to the following scale:

- No Days = 0

- 1-2 Days = 1
- 3-4 Days = 2
- 5-6 Days = 3
- Everyday = 4

4.2.10 SCORing Atopic Dermatitis (SCORAD)

SCORAD will be measured at each clinic visit, except the screening visit. The SCORAD grading system was developed by the European Task Force on Atopic Dermatitis (1993) and has been a standard tool to assess the AD severity in clinical studies. Six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) will be selected to evaluate the AD severity. The overall BSA affected by AD will be evaluated (from 0 to 100%) and included in the SCORAD scores. Loss of sleep and pruritus will be evaluated by patients on a visual analog scale (0-10). The sum of these measures represents the SCORAD which can vary from 0 to 103.

4.2.11 Athens Insomnia Scale (AIS)

The severity of sleep disturbance will be self-assessed daily starting from baseline using the Athens Insomnia Scale (AIS).

The AIS is a self-administered psychometric instrument consisting of eight items. The first five items of the AIS (assessing difficulty with sleep induction, awakenings during the night, early morning awakening, total sleep time, and overall quality of sleep) correspond to Criterion A for the diagnosis of insomnia according to ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision), while the requirements of a minimum frequency (at least three times a week) and duration (1 month) of any complaint correspond to Criterion B of the ICD-10. The ICD-10 requirements of marked distress caused by the sleep problem and/or interference with ordinary activities of daily living (Criterion C) are covered through the strictly subjective nature of the response options for every item of the scale as well as through the content of the last three items pertaining to the next day consequences of insomnia (problems with sense of well-being, functioning, and sleepiness during the day).

Each item of the AIS can be rated 0-3.

The responders are requested to rate positively if they had experienced the sleep difficulty described in each item at least three times a week between the study visits (Soldatos et al. 2000).

The baseline AIS is defined as the prorated average of the AISs reported continuously for 7 days right before and on the baseline visit (i.e. study day -6 to day 1). For post-baseline AIS, the mean weekly worst itch AIS is calculated as the prorated average of the reported daily AIS within the week. For example, if there are 3 scores in a week, the prorated average = (score1 + score2 + score3)/3.

4.2.12 Patient Oriented SCORAD (PO-SCORAD)

The PO-SCORAD will be measured at each clinic visit, except the screening visit. The PO-SCORAD is the SCORAD completed by the patients themselves. It is a self-evaluation tool developed by the European Task Force on Atopic Dermatitis (2011). Six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) will be selected to evaluate the AD severity. The overall surface affected, loss of sleep and pruritus will also be evaluated by patients on a visual analog scale.

4.2.13 Study medication: Intake and duration of intake

The duration of intake of study medication will be calculated as day of last dispensed of study medication minus day of first dispensed of study medication plus one.

The intake of study medication will be calculated as the number of capsules dispense per visit.

4.2.14 Previous vs. concomitant medication

Previous medications are those medications taken at least once before the first treatment of the patient. Concomitant medications are those medications taken at least once at/after the first treatment of the patient.

4.2.15 Adverse events

AEs with onset during or after administration of first study medication (study day 1) are defined as treatment emergent.

5 Blind Data Review Meeting

A BDRM will be held prior to database hard lock/unblinding where ***AMS*** and Sponsor representatives will assess protocol deviations as major or minor with regard to their influence on any of the analysis variables and to determine patient inclusion in the analysis sets.

The ***AMS*** biostatistician will prepare blinded review listings. Deviations not apparent in the clinical database (e.g. findings during monitoring of the investigational site) will be contributed by the sponsor's clinical project leader.

The decisions of the BDRM will be documented in writing and will be approved by signature of the attendees and may potentially amend methodology/analysis set definitions planned in this SAP.

The discussion in the review meeting will include but may not be restricted to the following topics:

- Violations of the study protocol including violations of inclusion/exclusion criteria
- Identification of patients randomised but not treated
- Impact assessment of prohibited medications
- Patients without efficacy data
- Patients where blind was broken prior to formal unblinding of the study
- Procedural deviations at the trial sites which are not reflected in the clinical database
- Premature patient discontinuations (reason and timing).
- Patients with COVID-19
- Patients with Week 16 visit window violations
- Assessment of impact of the COVID19 pandemic on visits occurring during COVID19 pandemic vs. other visits

Full details on the reviews performed and the decisions made in the BDRM will be given in the BDRM protocol.

6 General Methodology

All analyses will be performed using SAS Version 9.4 or higher.

If not mentioned otherwise analyses will be stratified by treatment group displaying the following treatment groups (in this ordering): DS107, Placebo, Total. Therefore treatment will not be mentioned explicitly as stratification variable usually.

All eCRF data will be listed, therefore listings may not be mentioned explicitly.

In listings the patient's screening number will be used as the main patient identifier. Usually listings will be sorted by treatment, patient's screening number and (if applicable) visit/point in time.

6.1 Primary Endpoint Evaluation

The primary endpoint variables will be:

- the proportion of patients achieving an vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ from baseline to Week 16.
- the proportion of patients achieving EASI-75 (≥75% improvement from baseline) at Week 16.

Both primary endpoints will be analysed using a Generalised Linear Mixed Model (GLMM) with treatment arm, visit, their interaction treatment-by-visit, and baseline vIGA-AD™ value as factors, and with patient as random effect; this model will especially be used to estimate missing data and the treatment effects at Week 16 taking missing data into account. The primary analysis will be based on the FAS, and repeated for the PPS as a supportive sensitivity analysis. Success in either of the primary endpoints denotes successful proof of efficacy.

If rescue medication is used, the patient will be specified as a non-responder from the time the rescue is used.

The handling of missing data in regards with primary statistical analysis and further sensitivity analysis using the jump to reference method to estimate the de facto estimand and analysing patients who received rescue medication as treatment failures are described in section 4.1.5.

6.2 Descriptive, Exploratory Analyses

Categorical variables will be displayed by absolute and relative frequencies (percentages). Percentages for categorical variables will be based on all non-missing values (=100%). Percentages will be rounded to one decimal place and therefore, there may be occasions when the total of the percentages does not exactly equal 100%.

Continuous variables will be summarised with number of observations, mean, standard deviation, median, minimum, maximum and the 5%, 25%, 75% and 95% quantiles. These descriptive statistics will be calculated for absolute values and for absolute differences to baseline, where appropriate.

6.3 Subgroup analyses

The primary endpoint will be conducted also by subgroups. The following subgroups will be considered:

- Baseline IGA (3, 4)

Further subgroups may be defined in the BDRM protocol if reasonable.

7 Final analysis

The following chapter summarises all analyses planned for the analysis of data collected within this trial.

7.1 Demographic and other baseline characteristics

Analyses of demographic will be performed as described in chapter 6.2 with the Randomised Set, details of the used analysis sets are described in chapter 8. The analysis will only be displayed overall. The following variables will be analysed:

- Age at time of consent [years]
- Gender (male, female)
- Height [cm]
- Weight [kg]
- BMI [kg/m^2]
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Demographic data will be listed.

The incidence of previous and concomitant diseases ("Medical History") will be displayed by MedDRA primary System Organ Class (SOC) and Preferred Term for the FAS.

7.2 Efficacy - Primary Endpoint Evaluation

Descriptive statistics will be provided for the two primary endpoints separately with the FAS.

Both primary efficacy endpoints will be analysed as defined in chapter 6.1 with the FAS.

These analyses will be displayed not only overall but also by subgroups as defined in chapter 6.3. The overall analysis will be repeated in an exploratory sense with the PPS.

7.3 Efficacy - Secondary Endpoints Evaluation

All secondary efficacy analyses will be performed as described in chapter 6.2 with the FAS only.

IGA and EASI-75 responders at other time points will also be analysed using a GLMM model similar to that described in Section 6.1.

The efficacy variables and their changes from baseline will be summarized with descriptive statistics per treatment group and visit. This applies to the vIGA-AD^{TM}, EASI, NRS scores for

pruritus, DLQI, POEM, SCORAD, AIS and PO-SCORAD. Change from baseline endpoints will be analysed using Mixed Model with Repeated Measures (MMRM) with Treatment Arm, Visit and Treatment x Visit Interaction as a factors and baseline value as a covariate, to account for missing data. For vIGA-AD™ as a 5-level ordinal variable, mixed ordinal logistic regression will be used with factors defined as above and IGA at baseline as a factor too.

If rescue medication is used, the patient will be specified as a non-responder from the time the rescue is used.

The following parameters will be analysed as described above:

- Proportion of patients achieving a vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ in treated population compared to placebo population from baseline to Week 4, 8, 12, 18 and 20
- Change in proportion of patients achieving a vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ in treated population compared to placebo population from Week 16 to Week 18 and 20.
- Absolute proportion of patients achieving EASI-75 (≥75% improvement from baseline) in treated population compared to placebo population at Week 4, 8, 12, 18 and 20
- Change from baseline in vIGA-AD™ score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20
- Change from Week 16 in vIGA-AD™ score in treated population compared to placebo population to Week 18 and 20.
- Change from baseline in EASI in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20
- Change from Week 16 in EASI in treated population compared to placebo population to Week 18 and 20.
- Absolute proportion of patients achieving a decrease of at least 4 points in worst itch NRS in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20. The NRS endpoint should be recorded weekly (descriptive values), as defined in section 4.2.6 and p-values only provided for the weeks defined in the endpoint.
- Absolute proportion of patients achieving a decrease of at least 3 points in worst itch NRS in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20. The NRS endpoint should be recorded weekly (descriptive values), as defined in section 4.2.6 and p-values only provided for the weeks defined in the endpoint.
- Change from baseline in worst itch NRS in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20. The NRS endpoint should be recorded weekly (descriptive values), as defined in section 4.2.6 and p-values only provided for the weeks defined in the endpoint.
- Change from Week 16 in worst itch NRS in treated population compared to placebo population to Week 18 and 20. The NRS endpoint should be recorded weekly (descriptive values), as defined in section 4.2.6 and p-values only provided for the weeks defined in the endpoint.
- Absolute proportion of patients achieving EASI-50 (≥50% improvement from baseline) in treated population compared to placebo population at Week 4, 8, 12, 16, 18 and 20.

- Change from baseline in the Body Surface Area (BSA) affected by AD in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20.
- Change from Week 16 in the Body Surface Area (BSA) affected by AD in treated population compared to placebo population to Week 18 and 20.
- Change from baseline in the SCORing Atopic Dermatitis (SCORAD) score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20.
- Change from Week 16 in the SCORing Atopic Dermatitis (SCORAD) score in treated population compared to placebo population to Week 18 and 20.

7.4 Efficacy - Exploratory Endpoints Evaluation

All Exploratory efficacy analyses will be performed as described in chapter 6.2 with the FAS only.

Change from baseline for exploratory endpoints (vIGA-AD™, SCORAD, DLQI, POEM, AIS and PO-SCORAD) will be analysed using mixed model with repeated measures (MMRM) as described in chapter 7.3.

The following parameters will be analysed as described above:

- Absolut proportion of patients achieving a decrease of at least 2 points in vIGA-AD™ in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20.
- Change in proportion of patients achieving a decrease of at least 2 points in vIGA-AD™ from Week 16 to Week 18 and 20.
- Change from baseline in the Dermatology Life Quality Index (DLQI) score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20.
- Change from Week 16 in the Dermatology Life Quality Index (DLQI) score in treated population compared to placebo population to Week 18 and 20.
- Change from baseline in the Patient Orientated Eczema Measure (POEM) score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20.
- Change from Week 16 in the Patient Orientated Eczema Measure (POEM) score in treated population compared to placebo population to Week 18 and 20.
- Change in sleep quality assessment (Athens Insomnia Scale) in treated population compared to placebo population from baseline to Week 4, 8, 12, 16, 18 and 20. The AIS endpoint should be recorded weekly (descriptive values), as defined in section 4.2.11 and p-values only provided for the weeks defined in the endpoint.
- Change in sleep quality assessment (Athens Insomnia Scale) in treated population compared to placebo population from Week 16 to Week 18 and 20. The AIS endpoint should be recorded weekly (descriptive values), as defined in section 4.2.11 and p-values only provided for the weeks defined in the endpoint.
- Change from baseline in the Patient-Oriented SCORAD (PO-SCORAD) score in treated population compared to placebo population to Week 4, 8, 12, 16, 18 and 20.
- Change from Week 16 in the Patient-Oriented SCORAD (PO-SCORAD) score in treated population compared to placebo population to Week 18 and 20.

7.5 Safety Evaluation

Adverse Events

The analyses of AEs with onset on or after first administration of study medication ("treatment-emergent AEs") will be conducted with the Safety Analysis Set whereas AEs occurring before first application of study medication will only be listed within the Enrolled Set.

The incidence of AEs will be displayed by MedDRA primary SOC and Preferred Term. The counts in these analyses will reflect numbers of patients reporting one or more AE that map to the MedDRA SOC/preferred term.

For AEs with onset during or after administration of first study medication analysis will be performed for the following AE categories:

- All AEs
- Serious adverse events (SAEs)
- AEs with relationship to the study medication
- AEs leading to discontinuation from study (as documented on the AE page)

Furthermore, a summary table with the overall incidences of the above mentioned AEs will be created.

In addition, the analysis of all treatment emergent AEs will also be done by intensity (mild, moderate and severe) displaying patients who reported more than one intensity for one AE under the worst intensity reported.

Furthermore the analysis of AEs and SAEs will also be done by outcome (Recovered/Resolved, Recovering/Resolving, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Fatal and Unknown).

The number/percentage of patients with AEs will also be summarized by MedDRA primary SOC and Preferred Term for most frequent non-serious AEs (incidence of preferred term ≥ 5%). In this table, the Totals overall or by SOC will consider only those preferred terms with an incidence >=5%.

All listings will use the Enrolled Set and will include study day of AE onset and AE stop as well as MedDRA information. Note that treatment-emergent AEs are those AEs with an onset at study day 1 or later. Listings will be created for the following topics:

- All AEs
- SAEs
- AEs with relationship to the study medication
- Death (Serious criterion “fatal” or outcome “fatal” documented on the AE page)
- AEs leading to study discontinuation
- AEs before 1st administration of study medication

Vital signs

The analysis of vital sign parameters

- Systolic blood pressure [mmHg]
- Diastolic blood pressure [mmHg]
- Heart rate [beats per min]
- Body temperature [°C]
- Body temperature [°F]

will be performed as described in chapter 6.2 with the Safety Analysis Set (descriptive summary of absolute values and changes from baseline).

Physical Examination

The number and percentage of patients with performed physical examination and the number and percentage of patients with abnormalities during the physical examination will be given within the Safety Analysis Set.

Safety laboratory

The analyses of the safety laboratory will be performed as described in chapter 6.2 with the Safety Analysis Set. The parameters of clinical chemistry and haematology will be analysed in the standardised units reported by the central laboratory.

In addition the number and percentage of patients with normal values, abnormal values with clinical significance and abnormal values without clinical significance will be given for each parameter of clinical chemistry and haematology. The worst value per patient per study will be used.

Laboratory values outside the normal range will be listed in detail.

Additionally, the change of laboratory values in regard to the respective normal ranges (below, within and above) from baseline to the last value (up to week 26) will be displayed in shift tables for each parameter of clinical chemistry and haematology.

ECG data

The analysis of ECG parameters will be performed as described in chapter 6.2 with the Safety Analysis Set. The listing will also include linked AE verbatim(s) and medical history verbatim(s).

Further safety endpoints

Childbearing Status / Pregnancy test data and virology data will be listed only.

7.6 Further Analyses

If not stated otherwise, all further analyses will be performed as described in chapter 6.2 with the Safety Analysis Set.

Previous and concomitant medication

The incidence of previous and concomitant medication will be displayed by ATC (Anatomical Therapeutic Chemical) classification (level 1 and 2 and preferred term). The analysis will be performed separately for previous medications and concomitant medications for the Safety Analysis Set. The listing will include a flag indicating if a medication is P (Previous) or C (Concomitant) or PC.

Study medication

- Duration of intake of study medication [days]
- Number of capsules dispense

will be analysed as described in chapter 6.2 with the Safety Analysis Set.

Termination status at end of trial

The incidence and reason for premature study termination (Screening failure, AE, Patient decision (withdrawal of consent to participate), Investigator discretion, Patient lost to follow-up, Lack of efficacy, Pregnancy, Other reasons) will be analysed for the Enrolled Set, i.e. including screening failures and randomised patients, and Safety Analysis Set.

Patients discontinued prematurely will be listed.

The incidence and reason (Violation of Inclusion Criteria X, Violation of Exclusion Criteria Y, Other) for Screening failure will be summarised (using non-randomised subjects of the Enrolled Set only).

Study duration and analysis sets

The day of first patient in the study and last patient out of the study will be given for the Enrolled Set as well as for the Safety Analysis Set.

The number of patients in each analysis set will be given by centre and overall. All patients will be listed with their assignment to the analysis populations and if applicable the reason for exclusion from specific analysis sets.

Protocol violations

Protocol violations identified in the BDRM will be listed including the decision if these constitute a minor or major protocol violation.

8 Tables and Figures

Item No.	Title	Population	Content Description	Mock Table
14.1.1	**Patient disposition**			
14.1.1.1	Patient disposition	Enrolled Set	Descriptive statistics of number of patients in analysis populations by centre and overall	T1
14.1.1.2	Study duration	Enrolled Set	Date of first patient in and last patient out	T2
14.1.1.2.1	Study duration	SAS	Date of first patient in and last patient out	T2
14.1.2	**Demographic data**			
14.1.2.1	Demographic data I	Randomised Set	Descriptive statistics of continuous variables	T3
14.1.2.2	Demographic data II	Randomised Set	Frequency table of categorical variables	T4
14.1.3	**Medical history and baseline evaluation**			
14.1.3.1	Medical history / Concomitant diseases by MedDRA primary SOC and preferred term	FAS	Frequency Table	T5
14.2	**Efficacy**			
14.2.1	**Primary Endpoint**			
	vIGA-AD™ score			
14.2.1.1	vIGA-AD™ score by visit	FAS	Frequency table by visit	T4a
14.2.1.2	vIGA-AD™ score by visit and subgroup	FAS	Frequency table by visit and subgroup	T4a
14.2.1.3	vIGA-AD™ response by visit	FAS	Descriptive statistics by visit	T4a
14.2.1.4	vIGA-AD™ response by visit and subgroup	FAS	Descriptive statistics by visit and subgroup	T4a
14.2.1.5	vIGA-AD™ score proportion from baseline to week 16 (GLMM)	FAS	Proportion (n (%) of patients achieving an vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ from baseline to Week 16 using a Generalised Linear Mixed Model	T6.1 T6.2

14.2.1.5.1	vIGA-AD™ score proportion from baseline to week 16 (GLMM)	PPS	Proportion of patients achieving an vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ from baseline to Week 16 using a Generalised Linear Mixed Model	T6.1 T6.2
14.2.1.6	vIGA-AD™ score proportion from baseline to week 16 (GLMM) by subgroup	FAS	Proportion of patients achieving an vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ from baseline to Week 16 using a Generalised Linear Mixed Model by subgroup	T6.1 T6.2
14.2.1.7	Sensitivity analysis of vIGA-AD™ score proportion from baseline to week 16 (de facto estimand)	FAS	Jump to reference method to estimate the de facto estimand	T7.1 T7.2
14.2.1.8	Sensitivity analysis of vIGA-AD™ score proportion from baseline to week 16 (rescue medication)	FAS	Patients who received rescue medication will be evaluated as treatment failures	T6.1 T6.2
	EASI-75 score			
14.2.1.9	EASI score by visit	FAS	Descriptive statistics by visit	T3a
14.2.1.10	EASI score by visit and subgroup	FAS	Descriptive statistics by visit and subgroup	T3a
14.2.1.11	EASI-75 response by visit	FAS	Descriptive statistics by visit	T4a
14.2.1.12	EASI-75 response by visit and subgroup	FAS	Descriptive statistics by visit and subgroup	T4a
14.2.1.13	EASI-75 response from baseline to week 16 (GLMM)	FAS	Proportion of patients achieving EASI-75 (≥75% improvement from baseline) at Week 16 using a Generalised Linear Mixed Model	T6.1 T6.2

14.2.1.13.1	EASI-75 response from baseline to week 16 (GLMM)	PPS	Proportion of patients achieving EASI-75 (≥75% improvement from baseline) at Week 16 using a Generalised Linear Mixed Model	T6.1 T6.2
14.2.1.14	EASI-75 response from baseline to week 16 (GLMM) by subgroup	FAS	Proportion of patients achieving EASI-75 (≥75% improvement from baseline) at Week 16 using a Generalised Linear Mixed Model by subgroup	T6.1 T6.2
14.2.1.15	Sensitivity analysis of EASI-75 response from baseline to week 16 (de facto estimand)	FAS	Jump to reference method to estimate the de facto estimand	T7.1 T7.2
14.2.1.16	Sensitivity analysis of EASI-75 response from baseline to week 16 (rescue medication)	FAS	Patients who received rescue medication will be evaluated as treatment failures	T6.1 T6.2
14.2.2	**Secondary Endpoints**			
14.2.2.1	**vIGA-AD™ score**			
14.2.2.1.1	vIGA-AD™ score proportion from baseline to week 4, 8, 12, 18, 20 (GLMM)	FAS	Proportion of patients achieving an vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ from baseline to Week 4, 8, 12, 18 and 20 using a Generalised Linear Mixed Model	T6.1 T6.2
14.2.2.1.2	Change in vIGA-AD™ score proportion at follow-up (GLMM)	FAS	Change in proportion of patients achieving an vIGA-AD™ score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points in vIGA-AD™ from Week 16 to Week 18 and 20 using a Generalised Linear Mixed Model	T6.1 T6.2
14.2.2.1.3	Change in vIGA-AD™ score from baseline to week 4, 8, 12, 16, 18, 20 (MMRM)	FAS	Change in vIGA-AD™ score from baseline to week 4, 8, 12, 16, 18, 20 using Mixed Model with Repeated Measures	T8.1 T8.2

14.2.2.1.4	Change in vIGA-AD™ score at follow-up (MMRM)	FAS	Change in vIGA-AD™ score from week 16 to week 18 and 20 using Mixed Model with Repeated Measures	T8.1 T8.2
14.2.2.1.5	Change in vIGA-AD™ score (mixed ordinal logistic regression)	FAS	Change in vIGA-AD™ score using mixed ordinal logistic regression	T9.1 T9.2
14.2.2.2	**EASI score**			
14.2.2.2.1	EASI-75 proportion from baseline to week 4, 8, 12, 18, 20 (GLMM)	FAS	Proportion of patients achieving EASI-75 (≥75% improvement from baseline) at Week 4, 8, 12, 18 and 20 using a Generalised Linear Mixed Model	T6.1 T6.2
14.2.2.2.2	Change in EASI score from baseline to week 4, 8, 12, 16, 18, 20 (MMRM)	FAS	Change in EASI score from baseline to week 4, 8, 12, 16, 18, 20 using Mixed Model with Repeated Measures	T8.1 T8.2
14.2.2.2.3	Change in EASI score at follow-up (MMRM)	FAS	Change in EASI score from week 16 to week 18 and 20 using Mixed Model with Repeated Measures	T8.1 T8.2
14.2.2.2.4	EASI-50 proportion from baseline to week 4, 8, 12, 16, 18, 20 (MMRM)	FAS	Proportion of patients achieving EASI-50 (≥50% improvement from baseline) at Week 4, 8, 12, 18 and 20	T8.1 T8.2
14.2.2.2.5	Change in EASI score by visit	FAS	Descriptive statistics by visit	T3a
14.2.2.2.6	EASI-50 response by visit	FAS	Descriptive statistics by visit	T4a
14.2.2.3	**NRS**			
14.2.2.3.1	NRS 4 point decrease proportion (MMRM)	FAS	Proportion of patients achieving a decrease of at least 4 points in worst itch NRS from baseline to week 4, 8, 12, 16, 18, 20	T8.1 T8.2

14.2.2.3.2	NRS 3 point decrease proportion (MMRM)	FAS	Proportion of patients achieving a decrease of at least 3 points in worst itch NRS from baseline to week 4, 8, 12, 16, 18, 20	T8.1 T8.2
14.2.2.3.3	Change in NRS (MMRM)	FAS	Change from baseline in worst itch NRS to week 4, 8, 12, 16, 18, 20	T8.1 T8.2
14.2.2.3.4	Change in NRS at follow-up (MMRM)	FAS	Change from week 16 in worst itch NRS to week 18 and 20	T8.1 T8.2
14.2.2.3.5	NRS score by visit	FAS	Descriptive statistics by visit	T3a
14.2.2.3.6	Change in NRS score	FAS	Descriptive statistics	T3a
14.2.2.3.7	NRS 3 point decrease and NRS 4 point decrease	FAS	Descriptive statistics	T4a
14.2.2.4	**BSA**			
14.2.2.4.1	Change in BSA (MMRM)	FAS	Change from baseline in the body surface area affected by AD to week 4, 8, 12, 16, 18, 20	T8.1 T8.2
14.2.2.4.2	Change in BSA at follow-up (MMRM)	FAS	Change from week 16 in the body surface area affected by AD to week 18 and 20	T8.1 T8.2
14.2.2.4.3	Body Surface Area (Value, Change from Baseline, Change from Wk 16) by visit	FAS	Descriptive statistics of body surface area at baseline and week 4, 8, 12, 16, 18, 20	T3a
14.2.2.5	**SCORAD score**			
14.2.2.5.1	Change in SCORAD (MMRM)	FAS	Change from baseline in the SCORAD score to week 4, 8, 12, 16, 18, 20	T8.1 T8.2
14.2.2.5.2	Change in SCORAD at follow-up (MMRM)	FAS	Change from week 16 in the SCORAD score to week 18 and 20	T8.1 T8.2
14.2.2.5.3	SCORAD (Value, Change from Baseline, Change from Wk 16) by visit	FAS	Descriptive statistics by visit	T3a
14.2.2.6	**Exploratory Endpoints**			
	vIGA-AD™ score			

14.2.2.6.1	vIGA-AD™ score 2 point decrease proportion (MMRM)	FAS	Proportion of patients achieving a decrease of at least 2 points in vIGA-AD™ from baseline to Week 4, 8, 12, 16, 18 and 20	T8.1 T8.2
14.2.2.6.2	Change in vIGA-AD™ score 2 point decrease proportion at follow-up (MMRM)	FAS	Change in proportion of patients achieving a decrease of at least 2 points in vIGA-AD™ from Week 16 to Week 18 and 20	T8.1 T8.2
	DLQI score			
14.2.2.6.3	Change in DLQI score (MMRM)	FAS	Change from baseline in the DLQI score to week 4, 8, 12, 16, 18, 20	T8.1 T8.2
14.2.2.6.4	Change in DLQI score at follow-up (MMRM)	FAS	Change from week 16 in the DLQI score to week 18 and 20	T8.1 T8.2
14.2.2.6.5	DLQI score (Value, Change from Baseline, Change from Wk 16) by visit	FAS	Descriptive statistics by visit	T3a
	POEM score			
14.2.2.6.6	Change in POEM score (MMRM)	FAS	Change from baseline in the POEM score to week 4, 8, 12, 16, 18, 20	T8.1 T8.2
14.2.2.6.7	Change in POEM score at follow-up (MMRM)	FAS	Change from week 16 in the POEM score to week 18 and 20	T8.1 T8.2
14.2.2.6.8	POEM score (Value, Change from Baseline, Change from Wk 16) by visit	FAS	Descriptive statistics by visit	T3a
	Athens Insomnia Scale			
14.2.2.6.9	Change in sleep quality assessment (MMRM)	FAS	Change from baseline in sleep quality assessment (Athens Insomnia Scale) to week 4, 8, 12, 16, 18, 20	T8.1 T8.2
14.2.2.6.10	Change in sleep quality assessment at follow-up (MMRM)	FAS	Change from week 16 in sleep quality assessment (Athens Insomnia Scale) to week 18 and 20	T8.1 T8.2

14.2.2.6.11	Sleep quality assessment (Value, Change from Baseline, Change from Wk 16) by visit	FAS	Descriptive statistics by visit	T3a
	PO-SCORAD Score			
14.2.2.6.12	Change in PO-SCORAD score (MMRM)	FAS	Change from baseline in PO-SCORAD score to week 4, 8, 12, 16, 18, 20	T8.1 T8.2
14.2.2.6.13	Change in PO-SCORAD score at follow-up (MMRM)	FAS	Change from week 16 in PO-SCORAD score to week 18 and 20	T8.1 T8.2
14.2.2.6.14	PO-SCORAD (Value, Change from Baseline, Change from Wk 16) by visit	FAS	Descriptive statistics by visit	T3a
14.2.3	**Further Analyses**			
14.2.3.1	Previous medication	SAS	Descriptive statistics by ATC classification (level 1 and 2 and preferred term)	T10
14.2.3.2	Concomitant medication	SAS	Descriptive statistics by ATC classification (level 1 and 2 and preferred term)	T10
14.2.3.3	Reason for Termination	Enrolled Set	Frequency Table	T4
14.2.3.3.1	Reason for Termination	SAS	Frequency Table	T4
14.2.3.4	Screening failure	Non-randomised subjects of the Enrolled Set	Frequency Table	T4
14.3	**Safety**			
14.3.1	**Study medication**			
14.3.1.1	DS107 intake duration	SAS	Descriptive statistics	T3
14.3.1.2	Capsules	SAS	Descriptive statistics of number of capsules dispensed	T3
14.3.2	**Adverse events**			
14.3.2.1	Summary table of Adverse Events	SAS	Frequency table of patients and number of events per AE category	T11
14.3.2.2	Adverse Events by MedDRA SOC and preferred term	SAS	Frequency table	T12

14.3.2.3	Serious Adverse Events by MedDRA SOC and preferred term	SAS	Frequency table	T12
14.3.2.4	AEs related to DS107 by MedDRA SOC and preferred term	SAS	Frequency table	T12
14.3.2.5	AEs leading to study discontinuation by MedDRA SOC and preferred term	SAS	Frequency table	T12
14.3.2.6	AEs by SOC, PT and worst intensity	SAS	Frequency table	T13
14.3.2.7	AEs by SOC, PT and outcome	SAS	Frequency table	T13
14.3.2.8	SAEs by SOC, PT and outcome	SAS	Frequency table	T13
14.3.2.9	Most frequent non-serious adverse events by MedDRA SOC and preferred term	SAS	Frequency table	T13
14.3.5	**Vital signs**			
14.3.5.1	Vital signs	SAS	Descriptive Statistics	T3a
14.3.5.2	Change in vital signs from baseline	SAS	Descriptive Statistics	T3a
14.3.5.3	ECG	SAS	Descriptive Statistics	T4a
14.3.6	**Laboratory values**			
14.3.6.1	Clinical Chemistry & Haematology	SAS	Descriptive Statistics	T3a
14.3.6.2	Clinical Chemistry & Haematology per category	SAS	Frequency Table (number and percentage of patients with normal values, abnormal values with clinical significance and abnormal values without clinical significance)	T4a
14.3.6.3	Change in Clinical Chemistry & Haematology	SAS	Shift Table	T14
14.3.7	**Physical Examination**			
14.3.7.1	Physical examination	SAS	Frequency table of patients with physical examination (yes/no)	T4

14.3.7.2	Abnormalities during physical examination	SAS	Frequency table of patients with abnormalities during physical examination	T4
16	**Appendices**			
16.2	**Patient data listings**			
16.2.1	Patient disposition	Enrolled Set	Individual patient data listing to analysis sets by cohort including reasons for exclusions, if applicable	L1
16.2.2	Violations of inclusion/exclusion criteria	Enrolled Set (only patients with violations)	Individual patient data listing by cohort	L6
16.2.3	Discontinuation	Enrolled Set	Individual patient data listing including reasons for discontinuation	L2
16.2.4	Demographic data / Informed Consent / Randomisation	Randomised Set	Individual patient data listing by cohort	L3
16.2.5	Vital Signs	FAS	Individual patient data listing by cohort and visit	L6
16.2.6.1	vIGA-AD™ score	Enrolled Set	Individual patient data listing by cohort and visit	L6
16.2.6.2	EASI score	Enrolled Set	Individual patient data listing by cohort and visit	L6
16.2.6.3	NRS score	Enrolled Set	Individual patient data listing by cohort and visit	L6
16.2.6.4	BSA	Enrolled Set	Individual patient data listing by cohort and visit	L6
16.2.6.5	SCORAD	Enrolled Set	Individual patient data listing by cohort and visit	L6
16.2.6.6	DLQI score	Enrolled Set	Individual patient data listing by cohort and visit	L6
16.2.6.7	POEM score	Enrolled Set	Individual patient data listing by cohort and visit	L6
16.2.6.8	AIS	Enrolled Set	Individual patient data listing by cohort and visit	L6
16.2.6.9	PO-SCORAD score	Enrolled Set	Individual patient data listing by cohort and visit	L6

16.2.7	**Adverse Events Listings**			
16.2.7.1	Adverse events	Enrolled Set	Individual patient data listing by cohort	L4
16.2.7.2	Serious adverse events	Enrolled Set	Individual patient data listing by cohort	L4
16.2.7.3	AEs related to DS107	Enrolled Set	Individual patient data listing by cohort	L4
16.2.7.4	AEs leading to death	Enrolled Set	Individual patient data listing by cohort	L4
16.2.7.5	AEs leading to study discontinuation	Enrolled Set	Individual patient data listing by cohort	L4
16.2.7.6	AEs before first administration of DS107	Enrolled Set	Individual patient data listing by cohort	L4
16.2.8	**Listing of individual laboratory measurements**			
16.2.8.1	Laboratory values	SAS	Individual patient data listing of laboratory results (haematology, clinical chemistry)	L5
16.2.8.2	Laboratory values outside the normal range	SAS	Individual patient data listing of laboratory results outside the normal range	L5
16.2.9	**Other Listing**			
16.2.9.1	Physical examinations	SAS	Individual patient data listing by cohort and visit	L6
16.2.9.2	Medical History / Concomitant diseases	FAS	Individual patient data listing by cohort	L6
16.2.9.3	Childbearing status and Pregnancy test data	FAS	Individual patient data listing by cohort and visit	L6
16.2.9.4	Virology	FAS	Individual patient data listing by cohort	L6
16.2.9.5	ECG	FAS	Individual patient data listing by cohort and visit	L6
16.2.9.6	Study drug dispensed	SAS	Individual patient data listing by cohort and visit	L6
16.2.9.7	Patient diary compliance	SAS	Individual patient data listing by cohort and visit	L6
16.2.9.8	IMP accountability and IMP compliance	SAS	Individual patient data listing by cohort and visit	L6
16.2.9.9	Previous and Concomitant medication	FAS	Individual patient data listing by cohort	L6

16.2.9.10	Violations of inclusion/exclusion criteria	Enrolled Set (only patients with violations)	Individual patient data listing by cohort	L6
16.2.9.11	Protocol violations	SAS	Individual patient data listing by cohort	L6

9 References

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