STATISTICAL ANALYSIS PLAN

Project Number:	MOR106
Study Number:	MOR106-CL-204
Study Title:	A randomized, double-blind, placebo-controlled, multicenter Phase 2 study to evaluate the safety and tolerability of subcutaneous MOR106 administered concomitantly with topical corticosteroids for eight weeks, in adult subjects with moderate to severe atopic dermatitis.
Development Phase:	II
Status:	Final
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Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium
Document Author:	[redacted]
Biostatistician:	[redacted]
Clinical Study Lead:	[redacted]

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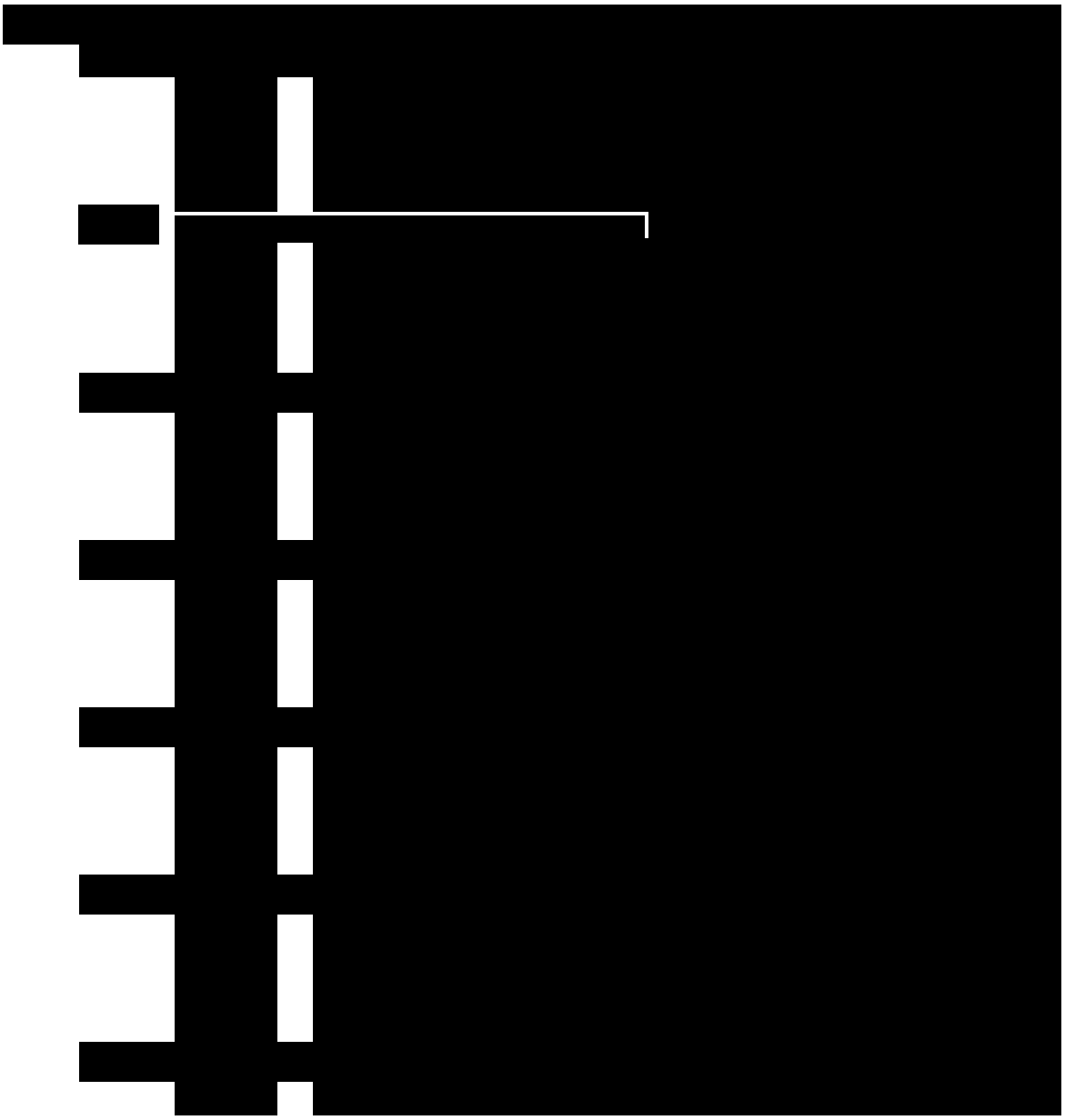

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ABBREVIATIONS COMMONLY USED

[redacted]	[redacted]
AD	Atopic Dermatitis
ADA	Anti-drug Antibody
ADaM	Analysis Data Model
ADY	Analysis relative day count
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the serum concentration-time curve
BLOQ	Below Limit of Quantification
BMI	Body Mass Index
[redacted]	[redacted]
CI	Confidence Interval
CRF	Case Report Form
CSP(A)	Clinical Study Protocol (Amendment)
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
[redacted]	[redacted]
ECG	Electrocardiogram
ED	Early Discontinuation
FAS	Full Analysis Set
GEE	Generalized Estimating Equations
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
[redacted]	[redacted]
IMP	Investigational Medicinal Product
ISR	Injection Site Reaction
ISRC	Independent Safety Review Committee
LD	Loading Dose
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measurement
NA	Not Available
NAP	Not Applicable
NC	Not Calculated
[redacted]	[redacted]
PD	Pharmacodynamics
PK	Pharmacokinetics
[redacted]	[redacted]
Q2W	Every two weeks
Q4W	Every four weeks
QTc	Corrected QT interval
QTcB	QT interval corrected for the heart rate using Bazett's formula

QTcF	QT interval corrected for the heart rate using Fridericia's formula
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
[redacted]	[redacted]
SOP	Standard Operation Procedure
[redacted]	[redacted]
TCS	Topical Corticosteroid
TCI	Topical Calcineurin Inhibitor
TEAE	Treatment-emergent Adverse Event
TLF	Tables, Listings, Figures
VAS	Visual Analogue Scale

DEFINITIONS OF TERMS COMMONLY USED

Analysis part	Section of the statistical analysis confining the analysis of a specific aspect in general terms, like safety, pharmacokinetics, etc.
Analysis period	Period of time during a study representing the time of exposure to a unique study drug or a unique combination of study drugs.
Analysis time point	Point in time within an analysis visit, usually obtained after a specific mapping and expressed in hours and/or minutes. It can also be expressed as a urine collection interval. Refers to the ATPT ADaM variable.
Analysis value	Result once established for analysis. Refers to the value stored in the AVAL or AVALC ADaM variables.
Analysis visit	Visit once established for analysis, usually obtained after a specific mapping and expressed in days. Refers to the AVISIT ADaM variable.
Study drug administration	Administration of study drug for the first time in the framework of the study.
Study drug	Investigational compound, or placebo, or positive control being tested or used as a reference in the study.
Treatment-emergent	Any (abnormal) condition appearing in a period of time under treatment which was not present at a referential point in time before, like an abnormality which was not present at baseline or an AE occurring after first study drug administration. Additional elements can apply to this definition in specific analysis sections and for specific purposes.

1. INTRODUCTION

This is a Phase II study to assess safety, tolerability and pharmacokinetics/exposure of MOR106.

The statistical analysis described by this analysis plan will be composed by tables, listings and figures (TLFs) presented in the following analysis parts:

- General subject information.
- [redacted]
- Pharmacokinetics (PK).
- Immunogenicity (ADA).
- Pharmacodynamics (PD) ([redacted]).
- Safety (adverse events, laboratory, electrocardiogram (ECG), vital signs and physical examination sections).

As a consequence of early termination of the development of MOR106 in atopic dermatitis for futility at the time point of MOR106-CL-201 interim analysis, this SAP constitutes an accordingly adapted version in terms of statistical evaluations of efficacy and pharmacodynamics endpoints.

1.1. CLINICAL STUDY PROTOCOL (CSP) AND CSP AMENDMENTS VERSION OVERVIEW

Final CSP Version	**Date**
CSP V3.0	15OCT2018

Final CSP Amendments	**Date**
CSP V4.0	25JUN2019
CSP Version 1.0 LVA GEO	24SEP2019 (first country-specific CSP (version 1.0), created for Latvia and Georgia, based on version 4.0 of the general CSP)

This SAP is based on the last version of the protocol.

1.2. STATISTICAL ANALYSIS PLAN (SAP) VERSION OVERVIEW

Final SAP Version	Date
V1.0	12 Mar 2020

2. STUDY OBJECTIVES AND DESIGN

2.1. STUDY OBJECTIVES

2.1.1. Primary Objective

The primary objective is to investigate the safety and tolerability of repeated subcutaneous (s.c.) doses of MOR106 administered concomitantly with topical corticosteroids (TCS) in subjects with moderate to severe atopic dermatitis (AD) who are candidates for systemic therapy.

2.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate the PK of repeated s.c. doses of MOR106 administered concomitantly with TCS.
- To monitor the occurrence of anti-drug antibodies (ADA) as a measure of immunogenicity after repeated s.c. doses of MOR106 administered concomitantly with TCS.

2.1.3. Other Objectives

The other study objectives are:

- [redacted]

2.2. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter Phase 2 study of repeated s.c. doses of 320 mg MOR106 or placebo, administered concomitantly with TCS. On Day 1, a loading dose (LD) will be administered (2 x 320mg MOR106, or placebo).

Adult subjects with moderate to severe AD who are candidates for systemic therapy will receive MOR106 or placebo every other week via s.c. injections (on Days 1, 15, 29, and 43). The 8-week treatment period, finishing on Day 57, is followed by a 16-week follow-up

period, finishing on Day 169. A total of 60 subjects (n=40 on MOR106 and n=20 on placebo) will be enrolled in this study.

Subjects will be randomized in a 2:1 ratio to receive one of the following treatments:

- MOR106 320 mg (2 mL at 160 mg/mL) every 2 weeks (Q2W) s.c. injection, with a loading dose (LD) of 640 mg (2 x 2mL at 160 mg/mL) s.c. injection on Day 1 (40 subjects).

- Corresponding placebo s.c. injections (20 subjects).

A total of 4 treatment days will be administered per subject. The end of the study is reached when the last follow-up visit or contact as planned according to the schedule of activities (see Section 6.10 of the protocol) of the last subject is performed.

2.3. STUDY ENDPOINTS

2.3.1. Primary Endpoints

The primary endpoints are the incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) through Day 169/early discontinuation (ED) visit.

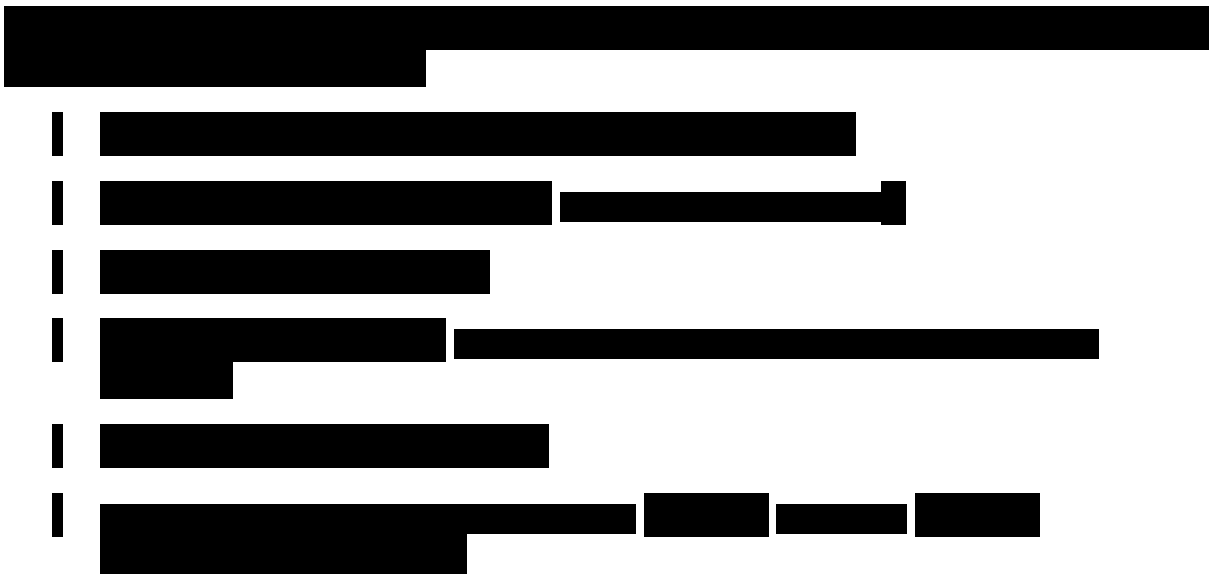
2.3.2. Secondary Endpoints

The secondary endpoints are:

- MOR106 serum concentrations after repeated s.c. administrations from baseline through Day 169/ED visit.

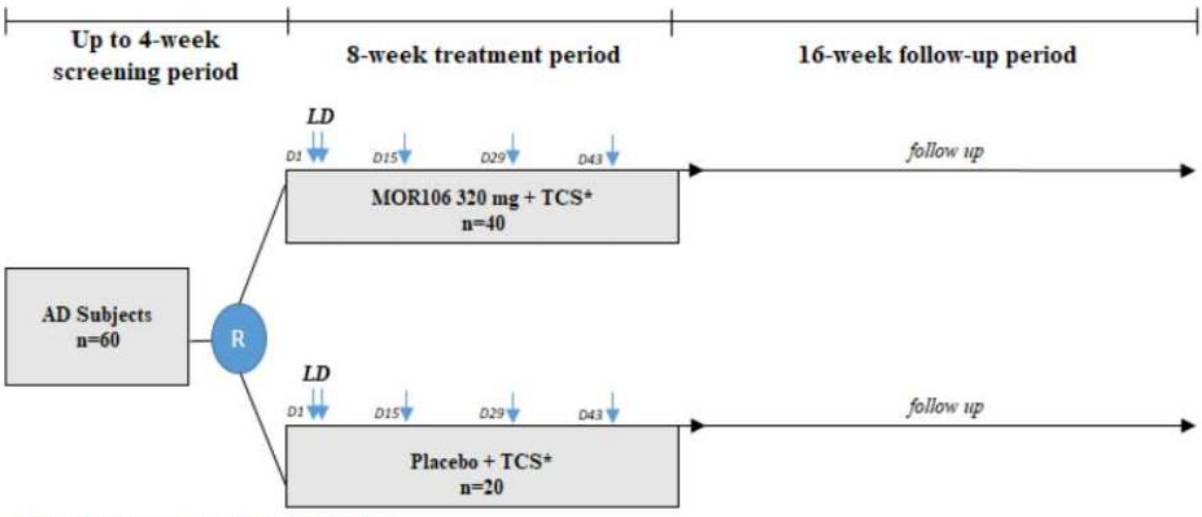
- Occurrence of ADA from baseline through Day 169/ED visit.

2.3.3. Other Endpoints



- [redacted]

2.4. SCHEMATIC DIAGRAM OF THE STUDY



R: Randomization on Day 1 (i.e. Baseline).

LD: Loading Dose (2x320 mg MOR106 or placebo) on Day 1.

**: TCS use according to approved label.*

2.5. SCHEDULE OF ACTIVITIES

The study scheduled of assessments is as follows (the sections mentioned refer the protocol):

EVENT	SCREENING PERIOD	TREATMENT PERIOD						FOLLOW-UP PERIOD							
Study Day (D)[1]	**D-28 to D-7**	**D1**	**D4 ±1**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2/ ETD[2]**	**D71 ±2**	**D85 ±2/**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D155 ±2**	**D169 ±2/ ED**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Informed consent (Section 10.4.2)	✓														
Inclusion/exclusion criteria (Section 4.5)	✓	✓													
Demographics (Section 6.3)	✓														
Medical history (Section 6.3)	✓														
(Targeted) Physical examination (Section 6.5.3)	✓	✓		✓[3]	✓	✓[3]	✓	✓[3]	✓	✓[3]	✓[3]	✓[3]	✓[3]	✓[3]	✓[3]
Vital signs (Section 6.5.4)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height (only at screening) and /or weight (Section 6.3)	✓				✓		✓								
12-lead ECG (Section 6.5.5)	✓	✓[4]				✓[4]	✓		✓		✓				✓
Pregnancy test[5] (Section 6.5.2)	✓	✓			✓		✓				✓				✓

[1] Visit dates are always calculated from Day 1 (unless subject discontinues early and attends an Early Treatment Discontinuation visit (ETD). If a subject has an ETD visit, the follow-up visits are performed 14, 28, 42, 56, 70, 84, 98 and 112 days after the ETD visit.
[2] Subject who are discontinued from treatment during the treatment period will perform Day 57/ETD visit (14 days after the last dose) as the last visit in the treatment period before entering the follow-up period.
[3] During these study visits, a targeted physical examination, consisting of cardiovascular, respiratory, gastrointestinal, and skin examination will be performed.
[4] At Day 1, ECG to be taken before dosing (triplicate ECGs) and approximately 1 hour after dosing. At Day 43, single ECG before dosing and approximately 1h after dosing.
[5] Females of childbearing potential only. Serum pregnancy test at screening, urine test before dosing on Day 1 and at all indicated time points thereafter.

EVENT	SCREENING PERIOD	TREATMENT PERIOD						FOLLOW-UP PERIOD							
Study Day (D)[1]	**D-28 to D-7**	**D1**	**D4 ±1**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2/ ETD[2]**	**D71 ±2**	**D85 ±2/**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D155 ±2**	**D169 ±2/ ED**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Clinical laboratory safety tests (incl. hematology, biochemistry and urinalysis), prior to injection on dosing days (Section 6.5.2)	✓	✓		✓	✓	✓	✓		✓			✓		✓	✓
Serology (Section 6.5.2)	✓														
[redacted]	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]		✓		✓	✓	✓	✓	✓		✓		✓		✓	✓
Train and check compliance of e-diary use	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]	Recording twice daily throughout study														
e-diary: TCS use	Recording daily throughout study														
e-diary: emollient use	Recording twice daily throughout study														
Provide Subject Participation Card (Section 10.2.4)	✓														
Skin swab (lesional and non-lesional) (Section 6.8.2)		✓					✓								✓
[redacted]		✓[6]					✓[6]								

[redacted]

EVENT	SCREENING PERIOD	TREATMENT PERIOD						FOLLOW-UP PERIOD							
Study Day (D)[1]	**D-28 to D-7**	**D1**	**D4 ±1**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2/ ETD[2]**	**D71 ±2**	**D85 ±2/**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D155 ±2**	**D169 ±2/ ED**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
[redacted]		✓					✓								✓
Immunogenicity assessment (ADAs; prior to injection on dosing days) (Section 6.6)		✓			✓		✓		✓		✓		✓		✓
PK blood samples (Section 6.5.6.1)		✓[7]	✓	✓[7]	✓[7]	✓[7]	✓	✓	✓	✓	✓	✓	✓	✓	✓
PD and biomarker blood samples, (prior to injection on dosing days) (Section 6.7)		✓			✓		✓		✓		✓		✓		✓
Randomization (Section 4.6.1)		✓													
IMP dosing (Section 5.2)[8]		✓		✓	✓	✓									
Injection site reactions (Section 6.5.6.1)		✓	✓	✓	✓	✓	✓								
(S)AE assessment (Sections 6.5.1, 9.2)	Throughout the study														
Prior/Concomitant medications (Section 4.5.3.2)	Throughout the study														

[7] PK samples have to be taken before injection and 1 hour after the injection (+/- 10 minutes) on Day 1. Samples have to be taken before injection on Days 15, 29, and 43.
[8] A loading dose, consisting of two consecutive injections will be performed on Day 1.

3. DEFINITION OF ANALYSIS POPULATIONS

The following subject populations will be determined for this statistical analysis.

The analysis population featuring in each TLF will be printed in a subtitle.

3.1. ALL SCREENED SUBJECTS

All subjects who signed and dated an ICF and underwent screening assessments to check whether or not they are eligible to participate in the clinical study.

3.2. ALL RANDOMIZED SUBJECTS

All enrolled subjects who underwent all screening assessments and were found to be eligible for the clinical study and who were randomized into the clinical study.

3.3. SAFETY AND IMMUNOGENICITY ANALYSIS SET

All randomized subjects who received at least one dose of investigational medicinal product (IMP). This population will be named safety analysis set in the TLFs.

3.4. FULL ANALYSIS SET

All randomized subjects who received at least one dose of IMP.

3.5. PHARMACOKINETIC ANALYSIS SET

Subset of the safety set, selecting all subjects who have available and evaluable MOR106 serum concentration data (e.g. excluding all protocol deviations or AEs that may have an impact on the PK analysis).

4. TREATMENT GROUPS

Subjects being assigned to or actually receiving a common treatment during a period of time in this study, constitute a treatment group for analysis.

4.1. CONSIDERATION OF THE PLANNED VERSUS THE ACTUAL TREATMENT

The treatment group as assigned by the randomization will be used in all analyses (i.e., as-randomized analysis) except the PK analyses where the actual treatment will be used. Cross-treated subjects will be listed separately.

4.2. DEFINITION OF TREATMENT GROUP LABELS

Treatment groups will be labeled as follows over the whole statistical analysis:

- Placebo Q2W s.c.
- MOR106 320 mg Q2W s.c.

4.3. TOTALS OVER TREATMENT GROUPS

Calculation of totals over all treatment groups will be presented only in tables and only in the general subject information (e.g. baseline, prior medication, accounting) of the analysis.

5. DEFINITION OF ANALYSIS PERIODS, OF ANALYSIS TIME POINTS, AND OF BASELINE

5.1. ANALYSIS PERIODS FOR NON-VISIT DATA

These analysis periods are to be used for allocation of events into periods (e.g., adverse events).

Analyses Periods for Non-Visit Data

Analysis period	Start period	End Period
Screening	Date of signing the ICF, with 00:00 added as time part.	1 minute before the date/time of first dose of study medication*
Treatment	First dose of study medication date/time*	Last dose of study medication date + 30 days, with 23:59 added as time part.#
Follow-up	Last dose of study medication date + 31 days, with 00:00 added as time part#	Study discontinuation date, with 23:59 added as time part.
* For endpoints without time collected, all assessments done on the day of the first dose will be assigned to the treatment period. # Time midnight is used as switch point to conservatively assign endpoints to the treatment period if on the date of last dose of study medication + 30 days.		

Note that the last analysis period in case of early discontinuation will always be ended by the study discontinuation date (date of last contact in the study).

5.2. ALGORITHM OF ALLOCATING VISITS TO TIME WINDOWS

For the efficacy, PK, PD and safety assessments, all data (including data obtained at unscheduled visits) will be placed into time windows based on the relative day (ADY) of the assessment, according to the following allocation tables:

Time windows for study drug administration:

Time point label	Target day	Interval lower bound	Interval upper bound
Day 1	1	1	1
Day 15	15	2	22
Day 29	29	23	36
Day 43	43	37	50
Day > 43[1]	NA	51	+INF
[1] This time point will be only listed.			

Time windows for PK:

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 1 (1h post-dose)[2]	1	1	1
Day 4	4	2	10
Day 15	15	11	22
Day 29	29	23	36
Day 43	43	37	50
Day 57	57	51	64
Day 71	71	65	78
Day 85	85	79	92
Day 99	99	93	106
Day 113	113	107	120
Day 127	127	121	134
Day 141	141	135	148
Day 155	155	149	162
Day 169	169	163	176
Day > 169[3]	NA	177	+INF

[1] Baseline will be defined as the last measurement before the start of IMP.

[2] For Day 1 (1h post-dose), no time window is defined. The visit as recorded in the CRF will be used, time of the assessment will be used to ensure that it was done post-dose.

[3] This time point will be only listed.

Time windows for [redacted] vital signs and physical examination:

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 15	15	2	22
Day 29	29	23	36
Day 43	43	37	50
Day 57	57	51	64
Day 71	71	65	78
Day 85	85	79	92
Day 99	99	93	106
Day 113	113	107	120
Day 127	127	121	134
Day 141	141	135	148
Day 155	155	149	162
Day 169	169	163	176

Time point label	Target day	Interval lower bound	Interval upper bound
Day > 169[2]	NA	177	+INF
[1] Baseline will be defined as the last measurement before the start of IMP. [2] This time point will be only listed.			

Time windows for weight:

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 29	29	2	43
Day 57	57	44	71
> Day 57[2]	NA	72	+INF
[1] Baseline will be defined as the last measurement before the start of IMP. [2] This time point will be only listed.			

Time windows for ECG:

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 1 (1h post-dose) [2]	1	1	1
Day 43 (pre-dose) [3]	43	2	50
Day 43 (1h post-dose) [2]	43	2	50
Day 57	57	51	71
Day 85	85	72	99
Day 113	113	100	141
Day 169	169	142	176
> Day 169[4]	NA	177	+INF
[1] Baseline will be defined as the last measurement before the start of IMP. [2] 1h post-dose assessment, no time window is defined. The visit as recorded in the CRF will be used, time of the assessment will be used to ensure that it was done post-dose. [3] Pre-dose assessment, no time window is defined. The visit as recorded in the CRF will be used, time of the assessment will be used to ensure that it was done pre-dose. [4] This time point will be only listed.			

Time windows for safety laboratory tests:

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 15	15	2	22
Day 29	29	23	36
Day 43	43	37	50
Day 57	57	51	71
Day 85	85	72	106

Time point label	Target day	Interval lower bound	Interval upper bound
Day 127	127	107	141
Day 155	155	142	162
Day 169	169	163	176
> Day 169[2]	NA	177	+INF
[1] Baseline will be defined as the last measurement before the start of IMP. [2] This time point will be only listed.			

Time windows for [redacted]

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 15	15	2	22
Day 29	29	23	36
Day 43	43	37	50
Day 57	57	51	64
Day 71	71	65	85
Day 99	99	86	113
Day 127	127	114	141
Day 155	155	142	162
Day 169	169	163	176
> Day 169[2]	NA	177	+INF
[1] Baseline will be defined as the last measurement before the start of IMP. [2] This time point will be only listed.			

Time windows for pregnancy test:

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 29	29	2	43
Day 57	57	44	85
Day 113	113	86	141
Day 169	169	141	176
> Day 169[2]	NA	177	+INF
[1] Baseline will be defined as the last measurement before the start of IMP. [2] This time point will be only listed.			

Time windows for [redacted]

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 57	57	2	64
> Day 57[2]	NA	65	+INF
[1] Baseline will be defined as the last measurement before the start of IMP. [2] This time point will be only listed.			

Time windows for immunogenicity (ADA), PD and biomarkers:

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 29	29	2	43
Day 57	57	44	71
Day 85	85	72	99
Day 113	113	100	127
Day 141	141	128	155
Day 169	169	156	176
> Day 169[2]	NA	177	+INF
[1] Baseline will be defined as the last measurement before the start of IMP. [2] This time point will be only listed.			

Time windows for injection site reactions:

Time point label	Target day	Interval lower bound	Interval upper bound
Day 1	1	1	1
Day 4	4	2	10
Day 15	15	11	22
Day 29	29	23	36
Day 43	43	37	50
Day 57	57	51	64
Day > 57[1]	NA	65	+INF
[1] This time point will be only listed.			

Time windows for skin swab:

Time point label	Target day	Interval lower bound	Interval upper bound
Baseline[1]	1	-INF	1
Day 57	57	2	113
Day 169	169	114	176
> Day 169[2]	NA	177	+INF
[1] Baseline will be defined as the last measurement before the start of IMP. [2] This time point will be only listed.			

Tables and figures will present the time points, not the visits. Listings will display the time points as recorded in CRF and as derived per the above time windows.

5.3. SELECTION OF VISITS

In case there are multiple measurements within a post-baseline time window, the one closest to the target day will be selected for the analyses. If there are multiple measurements at the same distance of the target day (meaning: equal ABS[ADY – target day]), then the one latest in time will be selected. If multiple measurements are taken on the same day, the mean of these values will be used. All data will be presented in listings with a flag if they were used in the analysis.

5.4. CALCULATION OF RELATIVE DAYS AND DURATIONS

The timing of an assessment or event (start or stop) relative to a referential date will be calculated as follows:

ADY (day) = concerned date – reference date (+ 1 day only when the concerned date is the same or later than the reference date)

Where:

- ADY is the analysis relative day count;
- *Concerned date* is an assessment visit date, or the start or stop date of an event;
- *Date* implies a complete date (day, month and year available);
- *Reference date* default is the date of first administration of study drug, unless otherwise specified.

Provided the resolution of the inputs (and respective unit) are adapted, the general terms of this formula also apply when similar relative timings are required in another time resolution, like in minutes.

Durations will be calculated in a similar way as:

Duration (days) = end date – start date + 1.

5.5. DEFINITION OF BASELINE

For each individual parameter, the last available result before the date and time of first study drug administration, whichever this assessment is, constitutes the reference assessment, i.e. baseline.

For electrocardiogram (ECG), the baseline is defined as the mean of the last recorded triplicate before the first study drug administration. If no triplicate is available before the first dose of study medication intake, the last ECG value will be considered as baseline.

6. SELECTION OF DATA RECORDS FOR ANALYSIS

All reported events, and all assessments without missing results will be used in the statistical analysis. However, the next specific exclusions will be done in some specific applications.

6.1. RECORDS HAVING EXTREME VALUES

Records yielding extreme results will be used for analysis in the general subject information, efficacy and safety parts of the analysis, even when these results are unusual or seemingly impossible.

In the PK/ part of the analysis, exclusion of abnormal PK concentration results/ will be formally discussed and determined after data base lock and before running the PK analysis, and documented in the PK/ Data Review Report.

6.2. REPEATED ANALYSIS VISITS AND ANALYSIS TIME POINTS

After baseline and except if unscheduled or being part of a specific profile, no replications of analysis visits or analysis time points should exist. Specifications for unscheduled analysis visits are described in the next section.

6.3. UNSCHEDULED ANALYSIS VISITS

Refer to sections 5.2 and 5.3.

6.4. SELECTION OF VALUES PROVIDED IN DIFFERENT UNITS

When values like results or normal limits are provided in conventional original units as well as in standardized units, only the expressions in standardized units will be considered for all analysis purposes. Data stored in original, conventional units will be disregarded.

7. HANDLING OF DATA

7.1. HANDLING OF MISSING DATA

7.1.1. Missing Records or Missing Values

No imputations will be done in case of missing records (visits) or missing values like results, normal limits etc.

7.1.2. Missing Dates or Times or Partially Known Dates or Times

No imputations will be done in case of missing date(time) fields, nor for the missing parts of partially known date(time) fields. If this causes imprecisions, a worst-case consideration will be done, like assuming persistence if an end date is missing, or replicating records over different analysis periods.

7.2. HANDLING OF SECONDS IN TIME FIELDS

The analysis will consider times only in hours and minutes. Seconds in the time of a record, if any, will be cut-off before analysis and disregarded.

7.3. CALCULATION AND PRESENTATION OF DESCRIPTIVE STATISTICS

Any descriptive statistics (and summary graphics) for continuous parameters will be printed only when the number of observations is two or more, except for PK analysis where specific rules are described below.Single observations will only be listed.

In the general subject information, efficacy and safety parts of the analysis, descriptive statistics will include:

- the number of non-missing observations (n);
- the arithmetic mean;
- the standard error (SE);
- the standard deviation (SD);
- the median;
- the minimum and maximum values;
- 95% confidence interval of the mean (only when requested).

For each parameter concerned, the number of decimal places printed for all descriptive statistics will be the same maximum number of decimals of the actual analysis values of the parameter, except:

- mean, median, confidence interval of the mean: one more decimal place;
- SD, SE: two more decimal places.

For PK part of the analysis, descriptive statistics will include:

- the number of non-missing observations (n);
- the number of data points above the limit of quantification (only applicable for concentrations);
- the arithmetic mean;
- the standard error (SE)
- the standard deviation (SD)
- the median;
- the minimum and maximum values;
- the coefficient of variation (CV%)
  = 100 x (standard deviation/arithmetic mean);
- the geometric mean
  = exp(arithmetic mean of ln-transformed data);
- the geometric coefficient of variation (geometric CV%)
  = 100 x $\sqrt{e^{(standard\ deviation\ of\ ln-transformed\ data)^2} - 1}$

If less than 50% of the subjects have quantifiable values, only the number of subjects with data, number of data points above the lower limit of quantification (LLOQ), the arithmetic mean, median, minimum, and maximum will be presented with the original calculated value. The other descriptive statistics will be listed as “NC” (not calculated).

If the calculated mean is below the lower limit of quantification (BLOQ), then it will be presented as “BLQ”.

The concentration levels will be presented in the original unit. Concentrations will be presented with:

– 2 decimals for values < 10
– 1 decimal for values > 10 and < 1000
– No decimals for value > 1000.

The descriptive statistics should be rounded to the same number of decimals as the individual values.

7.4. PRESENTATION OF INFERENTIAL STATISTICAL ANALYSIS

Refer to section 10 for more details.

7.5. CALCULATION AND PRESENTATION OF FREQUENCIES

Frequencies of categorical parameters will be calculated only for the actually observed cases. All observed frequencies from n = 1 on will be printed.

7.6. CALCULATION AND PRESENTATION OF PERCENTAGES

Frequencies and percentages will be generated for categorical parameters. Only non-missing values will contribute to the denominator when computing percentages.

The default denominator is the number of subjects in a treatment group, but can be further restricted as applicable. The denominator used should always be described in footnotes.

7.7. CATEGORIZATION OF RESULTS OF CONTINUOUS PARAMETERS

Categorization of the results of continuous parameters may apply in different sections of the analysis. Categorizations will always be determined after the analysis values of the parameters concerned have been established. Rounding of analysis values will not be done.

7.8. HANDLING OF VALUES BELOW OR ABOVE A THRESHOLD

- In the general subject information and in the safety part of the analysis: when results or normal limits of continuous parameters are expressed in the database as being below or above a detection limit (e.g. “<4”, “>1000”) and not available in pure

numerical form, the analysis value will be the value of the detection limit itself plus or minus one precision unit (e.g. 3, 1001, respectively). The values before this imputation will only be shown in listings.

- In the PK and PD [redacted] parts of the analysis:
    - Values below the quantification limit will be imputed by 0 for the calculation of descriptive statistics, PK analyses and graphical presentation except for the geometric mean and the geometric CV, where it will be imputed as LLOQ/2.
    - Values below the quantification limit will be listed as “BLQ”.

7.9. SOFTWARE, PROCEDURES AND STANDARDS

7.9.1. Software

SAS version 9.4 (or higher) will be used for programming.

Phoenix WinNonLin version 6.4 (or higher) will be used for PK derivations.

7.9.2. Procedures

This statistical analysis will comply with ICH regulations, in particular: (ICH-E3), (ICH-E6) and (ICH-E9).

The following Galapagos statistics, programming and pharmacokinetics SOPs will be followed:

- SOP-CLI-001: Developing Clinical Study Documents (version 2.0)
- SOP-BIOM-002: Managing Biostatistics Activities and Programming (version 1.0)

The following [redacted] statistics and pharmacokinetics SOPs will be followed:

– Statistics:
- BST002-SOP Version 2.0
- BST004-SOP Version 2.0
- BST005-SOP Version 2.0
- BST007-SOP Version 1.0
- PRG001-SOP Version 2.0

– PK:
- PK003-SOP Version 3.0
- PK004-SOP Version 2.0
- PK006-SOP Version 2.0

7.9.3. Standards for Data Storage and for Analysis Layout

The database source for this analysis is expected to follow the CDISC SDTM model.

The analysis derived datasets will follow the CDISC ADaM 2.1 model, based on the ADAMIG version 1.1.

The general layout of the tables, listings and figures of this analysis will follow the Sponsor Mock TLFs document (separate document).

8. STATISTICAL METHODS

8.1. PLANNED ANALYSES, PROTOCOL AMENDMENTS INCLUDED

The SAP will be finalized before the final analysis. All relevant data collected in this clinical study will be documented using summary tables, figures, and subject data listings.

8.1.1. Final Analysis

The full results will be summarized in a clinical study report (CSR) after all subjects have completed their study participation (i.e. Day 169 or discontinued earlier).

8.1.2. Sample Size

Refer to section 7.1 of the protocol.

8.1.3. General Statistical Considerations

In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data. Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 5% significance level.

No analysis by center or country will be performed, unless otherwise specified.

8.1.4. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for early discontinuation), protocol deviations, demographics, baseline characteristics, medical history, concomitant therapies will be analyzed descriptively based on the safety analysis set.

8.1.5. Analysis of Efficacy Parameters

Efficacy endpoint analyses will be performed using the FAS. For subjects who use rescue medication, all data collected after administration of the rescue medication will be excluded from efficacy analysis (this means that data collected on the day of rescue medication administration will be used for efficacy analysis). Subject data will be handled as if the subject left the study at the moment the rescue medication started. Efficacy assessment performed after the start of the rescue medication will only be listed.

Efficacy data [redacted]) will be summarized using descriptive statistics of actual values, changes from baseline, and percent changes from baseline, with 95% confidence intervals. Binary and categorical endpoints ([redacted]) will be presented by number (percent) of subjects per treatment group and visit.

Percent changes from baseline for continuous endpoints ([redacted]) will be analyzed using an mixed-effects model for repeated measures. The model will include

treatment and visit as fixed effects, country and baseline value (continuous) as covariates, and treatment-visit as interaction term.

Binary parameters ([redacted]) will be analyzed using a generalized estimating equation model. The model will include treatment and visit as fixed effects, country and baseline value (continuous) as covariates, and treatment-visit as an interaction term. Pairwise comparisons to placebo will be explored as well, without multiplicity correction.

The primary approach will be the observed case approach without imputation of missing data.

Additional exploratory analyses and graphical presentations may be performed when deemed useful to better understand the data.

All other efficacy endpoints will only be listed

8.1.6. Analysis of Immunogenicity Data

ADA status (positive/negative), ADA titer when ADA positive and potential drug interference in the assay when ADA negative (yes/no) will be listed by treatment group and time point. ADA status and potential drug interference will be also summarized.

8.1.7. Analyses of Safety Data

All safety analyses will be performed using the safety analysis set. Subjects will be analyzed according to the randomized treatment. All safety data collected on or after the first dose of IMP administration up to the last follow-up visit after the last dose of IMP, unless specified otherwise, will be summarized by treatment group according to the planned IMP. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs. Special attention will be paid to ISRs.

8.1.7.1. Extent of Exposure

A subject's extent of exposure to IMP will be generated from the IMP administration page of the CRF. Extent of exposure data will be summarized by treatment group. Extent of exposure to IMP will be expressed as the number of days between the first and last dose of IMP, inclusive, regardless of temporary interruptions in IMP administration and summarized by treatment group.

In addition, the number (percentage) of subjects who received all four treatment days, only three treatment days, etc. will also be summarized.

8.1.7.2. Adverse Events (AEs)

Clinical and laboratory AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. System Organ Class (SOC), High Level Group Term, High Level Term, Preferred Term, and Lower-Level Term will be attached to the clinical database.

The following AEs will be considered as TEAEs:

– All events during the complete study, with an onset on or after the IMP start will be counted.

Summaries (number and percentage of subjects and the number of events) of TEAEs by SOC and Preferred Term will be provided by treatment group. Subjects with TEAEs will also be summarized by causal relationship to IMP and severity. In addition, ISRs, skin related AEs, TEAEs leading to premature discontinuation of IMP and SAEs (including the non-treatment-emergent SAEs) will be summarized and listed.

Additionally, selected tables will also be created restricted to events with an onset date on or after the IMP start date and up to 30 days after last dose of IMP.

8.1.7.3. Clinical Laboratory Evaluations

Laboratory assessments will be analyzed descriptively. Changes from baseline (Day 1 pre-dose) and shifts according to normal ranges and CTCAE grades will be presented as well. Analyses will be done per treatment group.

8.1.7.4. Physical Examinations

Only abnormal post-baseline physical examination results will be listed.

8.1.7.5. Vital Signs

Vital signs will be analyzed descriptively. Changes from baseline (Day 1 pre-dose) and shifts according to normal ranges will be presented as well. Analyses will be done per treatment group.

8.1.7.6. 12-Lead Electrocardiogram

12-lead ECG will be analyzed descriptively. Changes from baseline (Day 1 pre-dose) and shifts according to normal ranges will be presented as well. Frequency analyses of subjects with a prolongation of more than > 60 ms change from baseline; > 500 ms for QT, QTcF and QTcB will be presented as well (for each parameter separately). Analyses will be done per treatment group.

8.1.7.7. Other Safety Assessments

Summary statistics for ISRs and skin related AEs are described in section 8.1.10.2.

8.1.8. Pharmacokinetic Analyses

For subjects in the PK analysis set, individual serum concentrations of MOR106 will be listed. Descriptive statistics will be calculated by day for the serum concentrations. Mean (± standard error) serum concentrations of MOR106 versus time will be plotted using both linear and semi-logarithmic scales.

MOR106 serum levels will be analyzed using population PK analyses, which will be described and reported separately.

8.1.9. Pharmacodynamic Analyses

PD data will only be listed using the subjects in the safety analysis set.

8.1.10. Additional Statistical Considerations

NAP.

8.2. CHANGES TO THE PLANNED ANALYSES, NOT COVERED BY THE PROTOCOL OR BY PROTOCOL AMENDMENTS

8.2.1. Changes before Database Lock and Justification

Per Sponsor's decision:

- ECG parameters normal ranges will be different to the ones mentioned in protocol to be consistent with other Sponsor's studies.
- For laboratory statistical analyses, CTCAE version 4.03 will be used instead of version 5.0 to be consistent with other Sponsor's studies.
- FAS population definition will be updated to be the same as the safety analysis set (due to the type of subjects and disease, it is not anticipated to have a difference between these populations).
- The safety analyses will be based on the randomized treatment and not on the actual treatment (cf. section 7.3.8 of the protocol).

As a consequence of early termination of MOR106 development in atopic dermatitis:

- Per Protocol analysis set will not be defined as no analyses will be performed on this set.
- The Primary Analysis will not be conducted as mentioned in the protocol.
- [redacted]
- [redacted]
- [redacted].
- Time-to-event analysis will not be performed
- [redacted]
- [redacted]

- [redacted]
- Terminal half-life $t_{1/2}$ will not be derived as mentioned in the protocol.
- [redacted]

8.2.2. Changes after Database Lock and Justification

Any planned analyses made after database lock will be documented in the CSR with a justification.

9. ANALYSIS OF GENERAL SUBJECT INFORMATION AND DEFINITION OF ANALYSIS TLFS

The analysis of general subject information will be descriptive. No inferential statistics will be computed.

9.1. SUBJECT DISPOSITION

Table 14.1.1.1: Subject disposition: Analysis populations

Tabulation per treatment group (and over all subjects) of the number of subjects in each of the analysis populations (screened, randomized, safety/immunogenicity, FAS and PK) defined for the study.

Population: all screened subjects.

Table 14.1.1.2: Subject disposition: Tabulation by country and site

Tabulation per treatment group (and overall) of the number of subjects in each of the countries and sites.

Population: all randomized subjects.

Table 14.1.1.3: Subject disposition: Tabulation of the number of subjects at each time interval

Tabulation per treatment group (and over all subjects) of the number of subjects in each visit/time interval.

Population: safety analysis set.

Table 14.1.1.4: Subject disposition: Study and treatment completion and discontinuation

Table per treatment group (and overall) of completion/discontinuation from study and from study medication and the reason for discontinuation.

Population: safety analysis set.

Table 14.1.1.5: Subject disposition: First and last dates in the study

Summary showing these key dates (regardless of treatment assignment):
- Date of the earliest ICF signed for this study;
- Date of first and of last screening visit (visits as reported in the database);
- Date of first study drug administration;
- Date of last physical visit performed in this study;
- Last date of contact with any subject in this study.

Population: all screened subjects.

Listing 16.2.1.1: Subject disposition: Randomization

Listing per subject showing subject number, ICF date, randomization number, randomization groups, randomization date and time and any information on code breaking:

- the reason for blind broken
- the number of days since first study dose of study medication at the time the subject is unblinded
- the AE preferred term (in case the unblind was due to an AE)
- (verbatim) explanation on the unblinding reason.

Discrepancies between planned and actual randomization groups will be flagged.

Population: all randomized subjects.

Listing 16.2.1.2: Subject disposition: Listing by country and site

Listing per treatment arm showing the country name, the site number and the list of subjects screened at this site.

Population: all randomized subjects.

Listing 16.2.1.3: Subject disposition: Number of days in study

Listing per treatment group, per subject and per time point showing subject number, the analysis populations inclusions, the actual study day of each visit and the whole study duration.

The whole study duration is derived as last date of contact – date of ICF + 1 day.

Population: safety analysis set.

Listing 16.2.1.4: Subject disposition: Study and treatment completion and discontinuation

Listing per treatment group and per subject showing the study completion or discontinuation status, the number of days since first study treatment administration at study termination and the subject's date of last contact in study. In case of discontinuation, the related reason and any available specifications will also be printed (i.e. the AE reported terms if the discontinuation was due to an AE, etc.).

The treatment completion or discontinuation status will be listed in a similar way.

Population: safety analysis set.

Listing 16.2.1.5: Subject disposition: Study analysis periods

Listing per treatment group and per subject showing the analysis periods, including the start and end dates of each analysis period and the date of first and last study drug administration.

Population: safety analysis set.

9.2. PROTOCOL DEVIATIONS AND ELIGIBILITY

Table 14.1.4.1: Protocol deviations: Summary of major protocol deviations

Frequency tabulation per treatment group (including the overall total) of major protocol deviations.

Population: safety analysis set

Listing 16.2.2.1: Major protocol deviations

Listing per treatment group and per subject showing all major protocol deviations that occurred during the study.

Population: safety analysis set.

Listing 16.2.2.2: Eligibility criteria: Violations

Listing per treatment group and per subject showing only the violated selection criteria for subjects treated (inclusion criteria not met, and exclusion criteria met), if any.

Population: safety analysis set.

Listing 16.2.2.3: Eligibility: Final statements

Listing per treatment group and per subject showing the eligibility statements at Screening and Day 1 (answers to the question "Did the subject meet all inclusion criteria and did not meet any exclusion criteria?").

Population: safety analysis set

9.3. SUBJECTS EXCLUDED FROM ANALYSIS PART

Note that for the PK data there is a specific PK data handling listing. PK is therefore not included in this section.

Listing 16.2.3.1: Subjects excluded from safety and full analysis sets

Listing of all subjects who were not treated due to any reason, showing them categorized as not treated subjects who were not randomized at all, and not treated subjects who were randomized (if randomization applies).

The study completion or discontinuation status, and any available reasons or specifications will also be printed next to each subject.

In the exceptional case a same subject participated more than once in this study due to any reasons (like first as a reserve subject not treated, and then again as a treated subject), the multiple participations of such a subject will be flagged and mentioned in this listing.

Population: all screened subjects (only subjects excluded from safety analysis set will be listed).

9.4. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

9.4.1. Parameters

The following parameters will be presented:

- Gender;
- Age (years) at the date of ICF signature;
- Year of birth: only listed;
- Date of study participation ICF signature: only listed;
- [redacted]
- [redacted];
- Race;
- Ethnicity;
- Height (cm) at baseline;
- Weight (kg) at baseline;
- Body mass index (BMI) at baseline;
- BMI categories at baseline:
  ≤ 18.5 kg/m²

]18.5, 25.0] kg/m²
]25.0, 30.0] kg/m²
> 30.0 kg/m²;

- Systolic blood pressure (mmHg) at baseline: only listed;
- Diastolic blood pressure (mmHg) at baseline: only listed;
- Heart rate (bpm) at baseline: only listed;
- Temperature (°C) at baseline: only listed;
- Childbearing potential for females: yes, no;
- Alcohol consumption: never, current, former;
- Nicotine consumption: never, current, former;
- Caffeine consumption: never, current, former.

Parameters mentioning 'at baseline' imply the selection of the last available result before the first study drug administration.

9.4.2. Analysis

Table 14.1.3.1: Demographic data: Descriptive statistics and tabulation

Continuous parameters: descriptive statistics per treatment group (including the overall total).

Categorical parameters: frequency tabulation per treatment group (including the overall total).

Population: safety analysis set.

Listing 16.2.4.1: Demographic data and baseline characteristics

Listing per treatment group and per subject of all demographic and baseline characteristic parameters.

Population: safety analysis set.

Listing 16.2.4.2: Substance use

Listing per treatment group and per subject of alcohol, nicotine and caffeine consumptions.

Population: safety analysis set.

9.5. BASELINE DISEASE CHARACTERISTICS

9.5.1. Parameters

- Duration of AD (years) = $\frac{(\text{date of signing ICF}) - (\text{date of initial diagnosis}) + 1}{365.25}$.
  If the date of initial diagnosis is incomplete, then the following rules will be applied:
  Missing day: use the first of the month.
  Missing month: use January;
- Duration of AD, categorized as:
  < 1 year,
  [1, 2[year,
  [2, 5[year,
  [5, 10[year,
  [10, 20[year,
  ≥ 20 year;
- Date of initial diagnosis: only listed;
- Age at time of initial diagnosis = $\frac{(\text{date of initial diagnosis}) - (\text{date of birth}) + 1}{365.25}$ (as day and month of the date of birth are not recorded in the database, this will be imputed to the 1st of July), categorized as:
  < 18 years,
  [18, 50[years,
  ≥ 50 years;
- [redacted];
- [redacted];
- [redacted];
- [redacted];
- Use of the following therapy (Yes/No):
  - Biologics therapy;
  - Non-biologic systemic therapy;
  - Phototherapy;
  - Topical treatment for AD;
- Any other AD: only listed.

9.5.2. Analysis

Table 14.1.3.2: Screening and baseline disease characteristics

Continuous parameters: descriptive statistics per treatment group (and overall).

Categorical parameters: frequency tabulation per treatment group (and overall).

Population: safety analysis set.

Listing 16.2.4.3: Screening and baseline disease characteristics

Listing per treatment group and per subject of all baseline disease characteristic parameters (date of initial diagnosis, duration of AD (flag the imputed durations), previous treatments for AD, other atopic disease), [redacted]

Population: safety analysis set.

9.6. MEDICAL HISTORY AND CONCURRENT DISEASES

Table 14.1.3.3: Medical history: Tabulation

Frequency tabulation per treatment group (and overall) of the system organ classes and preferred terms, selecting only medical conditions no longer present at the start of the study i.e. start of screening period.

Population: safety analysis set.

Table 14.1.3.4: Concurrent diseases: Tabulation

Frequency tabulation per treatment group (and overall) of the system organ classes and preferred terms, selecting only medical conditions still present at the start of the study i.e. start of screening period.

Population: safety analysis set.

Listing 16.2.4.4: Medical history

Listing per treatment group and per subject of the reported medical conditions no longer present at the start of the study i.e. start of screening period (including system organ class and preferred term from MedDRA coding dictionary).

Population: safety analysis set.

Listing 16.2.4.5: Concurrent diseases

Listing per treatment group and per subject of the reported medical conditions still present at the start of the study i.e. start of screening period (including system organ class and preferred term from MedDRA coding dictionary).

Population: safety analysis set.

9.7. PRIOR AND CONCOMITANT THERAPIES

9.7.1. Coding of Reported Terms

All prior and concomitant medications terms are expected to be coded using the WHO-DRUG coding dictionary (version March 2018 or later).

In the tables, the generic term will be used. The ATC classification will be used for analysis. Multiple records of the same generic term for the same subject with the same categorization will be counted only once. The table will therefore present subjects, not occurrences.

9.7.2. Categorization for Timing

All prior and concomitant therapy records will be categorized as follows, considering their dates:

- Prior only: when the record ended before the first study drug administration date.
- Concomitant only: when the record started on the same date or after the first study drug administration date until the last study drug administration + 30 days.
- Prior and concomitant: when the record started before the date of the first study drug administration, and ended on a date after the first study drug administration (or on the same date) or continued.

Records without a start date are assumed to have started before the date of the first study drug administration (records without an end date are assumed to be ongoing).

When the start or end dates of the prior and concomitant therapy records are incomplete, the date of the first study drug administration will be considered to the same level of information provided by the incomplete dates in order to categorize these records. This means a record only having month and year information will be categorized comparing only to the month and the year of the first study drug administration. The CRF question “Did the concomitant medication start prior to the first dose of study treatment?” will be also used for the categorization of the medication, if needed.

9.7.3. Calculation of the Relative Days

For both the start and the end dates of the concomitant therapy records, their day relative to the day of the first study drug administration will be calculated as described in section 5.4 of this SAP (calculation of relative days).

The relative day for a missing start date will be set to missing.

The relative day for an incomplete start or end date will be set to missing.

The relative day for a missing end date will be calculated up to the subject’s date of last contact in study, and will be printed as ‘>X days’.

9.7.4. Analysis

Table 14.1.3.5: Prior therapies: Tabulation

Frequency tabulation per treatment group (and overall) of the ATC 4 classes and generic terms. Only therapies defined above as 'prior only' or as 'prior and concomitant' are to be included.

Population: safety analysis set.

Table 14.1.3.6: Concomitant therapies: Tabulation

Frequency tabulation per treatment group (and overall) of the ATC 4 classes and generic terms. All therapies defined above as 'concomitant only' or 'prior and concomitant' are to be included.

Population: safety analysis set.

Listing 16.2.4.6: Prior and concomitant therapies

Listing per treatment group and per subject of all prior and concomitant therapy records, also showing their categorized timing as prior only, concomitant only or prior and concomitant.

When these records are linked to medical history or adverse events, these additional details (reported term of the medical history condition(s) or reported term of the adverse event(s), including their record ID numbers) will be printed as well.

Population: safety analysis set.

Listing 16.2.4.7: Prior and concomitant TCS/TCI therapies against atopic dermatitis

Same as Listing 16.2.4.6, only selecting TCS/TCI medications (i.e., Was this a TCS/TCI medication?="Yes").

Population: safety analysis set.

Listing 16.2.4.8: Concomitant intake of rescue atopic dermatitis medications

Same as Listing 16.2.4.6, selecting only rescue medications records (i.e., indication="Rescue AD medication").

Population: safety analysis set.

9.8. EXPOSURE TO STUDY MEDICATION AND COMPLIANCE

9.8.1. Derivations

A total of 4 treatment days with s.c. doses (including loading dose on day 1) are to be received by the subject.

Total treatment duration (days) = last dose of study medication date – first dose of study medication date + 1 day.

In addition, the number (%) of subjects who received >4, 4, 3, 2, 1 treatment days with s.c. injections will be tabulated.

9.8.2. Analysis

Table 14.1.5.1: Use of study medication: Descriptive statistics

Descriptive statistics per treatment group (and overall) of the total treatment duration (days).

Population: safety analysis set.

Table 14.1.5.2: Use of study medication: Tabulation of the number of injections received

Frequency tabulation per treatment group (and overall) of the number of treatment days with s.c. injections received: >4, 4, 3, 2, 1.

Population: safety analysis set.

Listing 16.2.5.1: Study drug administration

Listing per treatment group and per subject of all records related to the administration of study drug.

Population: safety analysis set.

Listing 16.2.5.2: Cross-treated subjects

Listing of subjects who took incorrect study medication (from another randomization group) for at least part of the treatment period, all prime therapy records are to be included to provide an overview of the amount of cross-treatment relative to the total treatment period. Results are to be presented by treatment and subject.

Population: safety analysis set.

Listing 16.2.5.3: Subjects for whom the injections were not administered per protocol

Listing of subjects who did not receive injection per-protocol (i.e. loading dose was not provided at day 1 or provided at another time point will be listed; reason for not providing the dose will be listed as well). Results are to be presented by treatment and subject.

Population: safety analysis set.

10. ANALYSIS OF EFFICACY AND DEFINITION OF ANALYSIS TLFS

The efficacy outputs will be generated using FAS.

10.1. DEFINITIONS, DERIVATION RULES AND PRESENTATION OF EFFICACY PARAMETERS

10.1.1. [redacted]

10.1.1.1. [redacted]

[redacted]

10.1.1.2. Tables

Table 14.2.1.1: [redacted]

[redacted]

Population: full analysis set.

Table 14.2.1.4: [redacted]

Population: full analysis set.

Table 14.2.1.5: [redacted]

Table 14.2.1.6: [redacted]

[redacted]

Population: full analysis set.

10.1.1.3. Figures

Figure 14.2.1.5: [redacted]

[redacted]

Population: full analysis set.

Figure 14.2.1.17: [redacted]

[redacted]

Population: full analysis set.

10.1.1.4. Listings

Listing 16.2.6.1: [redacted]

[redacted]

Population: full analysis set.

10.1.2. [redacted]

10.1.2.1. Derivations

[redacted]

[redacted]

10.1.2.2. Tables

Table 14.2.1.8: [redacted]

[redacted]

Population: full analysis set.

[redacted]

10.1.2.3. Figures

No figure will be provided for this parameter.

10.1.2.4. Listings

Listing 16.2.6.2: [redacted]

[redacted]

Population: full analysis set.

10.1.3. [redacted]

10.1.3.1. Derivations

[redacted]

10.1.3.2. Tables

Table 14.2.1.9: [redacted]

[redacted]

Population: full analysis set.

Table 14.2.1.11: [redacted]

[redacted]

Population: full analysis set.

10.1.3.3. Figures

Figure 14.2.1.15: [redacted]

[redacted]

Population: full analysis set.

Figure 14.2.1.17: [redacted]

Same figure as

[redacted].

Population: full analysis set.

10.1.3.4. Listings

Listing 16.2.6.3: [redacted]

[redacted]

Population: full analysis set.

10.1.4. [redacted]

10.1.4.1. Derivations

[redacted]

10.1.4.2. Tables

No table will be provided for this parameter.

10.1.4.3. Figures

No figure will be provided for this parameter.

10.1.4.4. Listings

Listing 16.2.6.4: [redacted]

[redacted]

Population: full analysis set.

10.1.5. [redacted]

10.1.5.1. Derivations

[redacted]

10.1.5.2. Tables

No table will be provided for this parameter.

10.1.5.3. Figures

No figure will be provided for this parameter.

10.1.5.4. Listings

Listing 16.2.6.5: [redacted]

[redacted]

Population: full analysis set.

10.1.6. [redacted]

10.1.6.1. Derivations

[redacted]

10.1.6.2. Tables

No table will be provided for this parameter.

10.1.6.3. Figures

No figure will be provided for this parameter.

10.1.6.4. Listings

Listing 16.2.6.6: [redacted]

[redacted]

Population: full analysis set.

10.1.7. [redacted]

10.1.7.1. Derivations

[redacted]

10.1.7.2. Tables

Table 14.2.1.19: [redacted]

[redacted]

Population: full analysis set.

10.1.7.3. Figures

Figure 14.2.1.37: [redacted]

Population: full analysis set.

10.1.7.4. Listings

Listing 16.2.6.7: [redacted]

Population: full analysis set.

Listing 16.2.6.8: [redacted]

Population: full analysis set.

10.1.8. [redacted]

10.1.8.1. Derivations

[redacted]

10.1.8.2. Tables

No table will be provided for this parameter.

10.1.8.3. Figures

No figure will be provided for this parameter.

10.1.8.4. Listings

[redacted]

10.1.9. [redacted]

10.1.9.1. Derivations

[redacted]

10.1.9.2. Tables

No table will be provided for this parameter.

10.1.9.3. Figures

No figure will be provided for this parameter.

10.1.9.4. Listings

[redacted]

11. ANALYSIS OF PHARMACOKINETICS AND DEFINITION OF ANALYSIS TLFS

11.1. DEFINITIONS, DERIVATION RULES AND PRESENTATION OF PK PARAMETERS

11.1.1. Available Data

Compound: MOR106 in serum (free drug levels).

11.1.2. PK Parameters and Derivation Rules

No PK parameters will be derived.

11.1.3. PK Derivation Rules

- Time deviation:
  - The actual sampling time will be used for graphical presentation of the individual data.
- Handling of BLOQ values:
  - Concentration BLOQ will be imputed according to the rules mentioned in section 7.8.
  - If the concentrations before the first quantifiable concentration time point is BLOQ, the concentration will be set to 0.
  - If the concentrations after the last quantifiable concentration time point is BLOQ, the concentration will be set to missing.
  - If there are embedded BLOQ values between quantifiable concentrations after the last dose on Day 43, these BLOQ values will be set to missing.
  - If there is a quantifiable concentration after 2 consecutive BLOQ values at the end of the profile after the last dose on Day 43, this quantifiable concentration will be set to missing.

Excluded data will be discussed in the PK Data Review (Appendix 16.1) and flagged in the TLFs.

11.1.4. Tables

Table 14.2.2.1: MOR106 serum concentrations (µg/mL): Individual data and descriptive statistics and time point

Subject data and descriptive statistics per analysis visit/time point of the serum concentrations will be displayed.

Population: PK analysis set.

11.1.5. Figures

Figure 14.2.2.5: MOR106 trough serum concentrations (µg/mL): Subject profile plots (linear-linear scale)

Subject profile plots of the MOR106 trough serum concentrations over time with all subjects on the same plot (up to Day 57 including only pre-dose timepoints and Day 57 results to be displayed on the same plot).

Population: PK analysis set.

Figure 14.2.2.6: MOR106 trough serum concentrations (µg/mL): Mean (+/- SE) concentration over time (linear-linear scale)

Arithmetic mean with SE of the MOR106 trough serum concentrations over time (up to Day 57 including only pre-dose timepoints and Day 57 results to be displayed on the same plot).

Population: PK analysis set.

11.1.6. Listings

Listing 16.2.7.1: PK data handling

Listing per treatment, subject and analysis visit/time point of any data issue.

Population: PK analysis set.

Listing 16.2.7.2: Actual PK blood sampling times (h)

Listing per treatment, subject and analysis visit/time point of the PK sampling times relative to the actual drug intake. Deviations from the scheduled sampling times of more than 10% will be flagged (for post-dose assessments), as well as pre-dose samples that were actually taken post-dosing.

Population: PK analysis set.

Listing 16.2.7.3: MOR106 serum concentrations (µg/mL): Individual data

Listing per treatment, subject and analysis visit/time point of all MOR106 serum concentration data.

Population: PK analysis set.

12. ANALYSIS OF IMMUNOGENICITY AND DEFINITION OF ANALYSIS TLFS

Table 14.2.3.1: Anti-MOR106 antibodies (ADA): Tabulation per treatment and time point

Frequency table of ADA status (positive/negative) and potential drug interference in the assay when ADA negative (yes/no) by treatment group at Day 1 and all post-dose time points.

Population: safety analysis set.

Listing 16.2.8.1: Anti-MOR106 antibodies (ADA): Full listing

Listing per treatment, subject and analysis visit/time point of ADA results, titer and potential drug interference.

Population: safety analysis set.

13. ANALYSIS OF PHARMACODYNAMICS AND DEFINITION OF ANALYSIS TLFS

13.1.1. Disease Status Definition

[redacted]

13.1.2. Tables

No table will be provided for these parameters.

13.1.3. Figures

No figure will be provided for these parameters.

13.1.4. Listings

Listing 16.2.9.3: [redacted]

[redacted], [redacted]

Population: safety analysis set.

14. ANALYSIS OF SAFETY AND DEFINITION OF ANALYSIS TLFS

The analysis of safety data will be descriptive. No inferential statistics will be computed.

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject (safety analysis set):

- Adverse events
- Non-drug related therapies
- Laboratory safety
- Electrocardiogram (ECG) investigations
- Vital signs
- Physical examination

14.1. ADVERSE EVENTS

14.1.1. Coding of Reported Terms

All adverse event terms are expected to be coded using the MedDRA coding dictionary (version 21.0 or higher).

All tables in this section will show the AE terms coded into preferred terms and system organ classes. Subject listings will also show the reported terms. All other coding levels will only be shown in a listing summarizing coding or when explicitly mentioned.

14.1.2. Definition of Treatment-emergent Adverse Events

All adverse events starting as of the point of administration of study drug (i.e. start date of dose administration for s.c. dosing) until the last contact of the subject are defined as treatment-emergent adverse events (TEAE).

All adverse events tables will only show TEAEs.

Adverse events starting before administration of study drug (not TEAEs) will only be listed.

If an AE starts before administration of study drug but worsens after then:

- Until the worsening, the AE will be considered as a non-TEAE;
- From the worsening, the AE will be considered as a TEAE.

But if an AE starts before administration of study drug and improves after the first dose, the AE will not be considered as a TEAE.

14.1.2.1. Combining of Events to be Able to Count Number of Events

A worsening is defined when one of the attributes of the events worsens (severity, seriousness, relationship or action taken). Worsenings observed after first dose of study medication of an event will be considered as a new event, improvements will not.

14.1.3. Allocation of Adverse Events to Analysis Periods

All adverse events records will be placed into analysis periods considering their start date(time), i.e. aiming to report the incidence of these events only in the analysis period during which they started.

The general rule for allocation of AEs to analysis periods follows:

Analysis period start date(time) ≤ AE start date(time) ≤ analysis period end date(time)

If the start date(time) of an AE is incomplete and to such a level preventing a clear allocation of the AE to one single analysis period, a worst-case consideration will be done aiming to allocate the AE record to one single analysis period, if possible. The CRF question “Did the adverse event start prior to the first dose of study treatment?” will also be considered for the analysis period allocation.

When a worst-case consideration is needed for allocation to analysis periods, the end date of the AE records, if and as available, should also be considered; if such AEs clearly end on a given point, this will exclude the possibility to allocate the AE to an analysis period after that point.

- An AE which according to the available information of its start date(time) could belong to the screening and to the treatment analysis period will only be placed in the treatment analysis period.

- An AE which according to the available information of its start date(time) could belong to the treatment analysis period and to the Follow-up analysis period will only be placed in the treatment analysis period.

14.1.4. Treatment Relatedness

Following (ICH-E3), the originally reported relatedness to study drug of an AE will be dichotomized as follows:

- Not study drug related: this includes the levels ‘unrelated’, ‘unlikely’ and ‘not applicable’.

- Study drug related: this includes the levels ‘possible’, ‘probable’ and ‘certain’ (includes, as a worst-case consideration, any missing drug relatedness).

This dichotomized relatedness will only be used in tables; relatedness as originally reported will only be listed.

14.1.5. Worst-case Selections

When cross-tabulating AE preferred terms versus an AE attribute (e.g., intensity), the worst-case is always applied within each subject, preferred term and analysis period, i.e., when a subject has multiple times the same AE preferred term in the same analysis period, then the subject is reported only once: only with the worst intensity. If this happens in two different analysis periods, the AE is reported twice: once in each analysis period.

CRF will collect the changes in AE. If there is a change of intensity, seriousness, drug relatedness or action taken, the worst category (by analysis period when applicable) will be considered for tables.

14.1.6. Adverse Event Onset Day and Duration

See section Calculation of Relative Days and Durations.

For each AE record, its onset day in study (the day of the AE start date relative to the date of administration of study drug), its onset day in the analysis period, and its duration in days will be calculated and shown only in listings.

These relative onset days, and the AE duration will be set to missing if the AE start date is incomplete or missing.

If the AE end date is incomplete, the AE duration will be set to missing.

If the AE end date is missing, the AE duration will be calculated until the date of last contact in the study for the concerned subject, printing such AE duration as '>X days'.

If the outcome of an AE is 'not resolved' or equivalent, the AE duration will be calculated with either the provided AE end date or until the date of last contact in the study for the concerned subject (whichever is earliest/available), also printing such duration as '>X days'.

Since worsenings of intensity, seriousness, drug relatedness or action taken are recorded in the CRF, two durations will be computated:

- The duration (days) of the individual event: the duration of the event until worsening or until resolution or until the date of last contact (whatever applies).

- The duration (days) of the overall event: the duration of the event until the end of the worsening or until resolution or until the date of last contact (whatever applies).

If there is no worsening, the individual event duration and the overall event duration will be equal. In case of worsening, for the event(s) stating for the worsening(s), only the individual event duration will be computed. For the initial event, both durations will be computed as for the events without worsening.

14.1.7. Calculation of Percentages

The denominator for all percentages will be the total number of subjects in each treatment group within the analysis period.

14.1.8. Tables

Analysis periods will be replaced by their respective treatment via the randomization list (i.e, an as-randomized allocation) in all tables and listings.

Table 14.3.1.1: Treatment-emergent adverse events: Summary table

Tabulation per treatment group of the incidence of subjects:

- With at least one treatment-emergent adverse event (TEAE);
- With at least one serious TEAE;
- With at least one ISR;
- With at least one skin related TEAE;
- With at least one ISR (Grade 3 or higher) or skin related TEAE;
- With at least one AE leading to death;
- With at least one mild TEAE as worst intensity per treatment;
- With at least one moderate TEAE as worst intensity per treatment;
- With at least one severe TEAE as worst intensity per treatment;
- With at least one life threatening TEAE as worst intensity per treatment;
- With at least one fatal TEAE as worst intensity per treatment;
- With at least one TEAE considered related to study drug;
- With at least one TEAE for which the study drug was temporarily stopped;
- With at least one TEAE for which the study drug was permanently stopped.

Population: safety analysis set.

Table 14.3.1.2: Treatment-emergent adverse events up to 30 days after last dose: Summary table

Same as Table 14.3.1.1, but restricted to events that started after start of study medication and up to 30 days after last dose.

Population: safety analysis set.

Table 14.3.1.3: Treatment-emergent adverse events: Tabulation of all adverse events

Incidence of subjects tabulation per treatment group of TEAE classified per system organ class and preferred term.

Population: safety analysis set.

Table 14.3.1.4: Treatment-emergent adverse events up to 30 days after last dose: Tabulation of all adverse events

Same as Table 14.3.1.3, but restricted to events that started after start of study medication and up to 30 days after last dose.

Population: safety analysis set.

Table 14.3.1.5: Treatment-emergent adverse events: Tabulation of all adverse events by preferred term

Incidence of subjects tabulation per treatment group of TEAE classified per preferred term.

Population: safety analysis set.

Table 14.3.1.6: Treatment-emergent adverse events up to 30 days after last dose: Tabulation of all adverse events by preferred term

Same as Table 14.3.1.5, but restricted to events that started after start of study medication and up to 30 days after last dose.

Population: safety analysis set.

Table 14.3.1.7: Treatment-emergent adverse events: Tabulation of all adverse events – Alphabetic order

Same as Table 14.3.1.3 but sorted by alphabetic order.

Population: safety analysis set.

Table 14.3.1.8: Treatment-emergent adverse events up to 30 days after last dose: Tabulation of all adverse events – Alphabetic order

Same as Table 14.3.1.3, but restricted to events that started after start of study medication and up to 30 days after last dose and sorted by alphabetic order.

Population: safety analysis set.

Table 14.3.1.9: Treatment-emergent adverse events: Tabulation per worst intensity

Cross-tabulation of incidence of subjects per treatment group of TEAE preferred terms classified per system organ class versus their intensity. Considering the worst-case intensity per TEAE preferred term and per subject in each treatment group.

Population: safety analysis set.

Table 14.3.1.10: Treatment-emergent adverse events: Tabulation of all treatment-related events

Same as Table 14.3.1.3, but restricted to the AEs categorized as related to study drug.

Population: safety analysis set.

Table 14.3.1.11: Treatment-emergent adverse events: Tabulation of treatment-related events per worst intensity

Same as Table 14.3.1.9, but restricted to the AEs categorized as related to study drug.

Population: safety analysis set.

Table 14.3.1.12: Treatment-emergent adverse events: Tabulation of all injection site reaction events

Same as Table 14.3.1.3, but restricted to the ISR events.

Population: safety analysis set.

Table 14.3.1.13: Treatment-emergent adverse events: Tabulation of all injection site reaction events per worst intensity

Same as Table 14.3.1.9, but restricted to the ISR events.

Population: safety analysis set.

Table 14.3.1.14: Treatment-emergent adverse events: Tabulation of all skin related events

Same as Table 14.3.1.3, but restricted to the skin related events.

Population: safety analysis set.

Table 14.3.1.15: Treatment-emergent adverse events: Tabulation of all skin related events per worst intensity

Same as Table 14.3.1.9, but restricted to the skin related events.

Population: safety analysis set.

Table 14.3.1.16: Treatment-emergent adverse events: Tabulation of all events for which the study or study treatment were discontinued

Same as Table 14.3.1.3, but restricted to the TEAEs for which the study treatment was permanently discontinued, or for which the study was discontinued.

Population: safety analysis set.

Table 14.3.1.17: Serious treatment-emergent adverse events: Tabulation for EudraCT reporting

Frequency tabulation per treatment group of serious TEAEs per system organ class and preferred term, showing both the number of subjects and events themselves.

Population: safety analysis set.

Table 14.3.1.18: Non-serious treatment-emergent adverse events: Tabulation for EudraCT reporting

Same as Table 14.3.1.17, but restricted to the non-serious TEAEs.

Population: safety analysis set.

Table 14.3.1.19: Non-serious treatment-emergent adverse events: Tabulation for EudraCT reporting of TEAEs occurring in at least 5% of the overall subjects

Same as Table 14.3.1.17, but restricted to the non-serious TEAEs.

All the lines from the table where there is at least 5% occurrence (of the subjects) of the overall subjects either at system organ class or at preferred term level will be displayed. If the system organ class line is selected but none of the associated preferred terms, then the system organ class will still be presented but without preferred terms.

Population: safety analysis set.

14.1.9. Figures

Figure 14.3.1.1: Treatment-emergent adverse events sorted by risk difference

Graphical presentation ordered by risk difference versus placebo, presenting for each preferred term on the left panel the proportion of subjects with at least one TEAE for the active and placebo group and in the right panel the treatment difference and its 95% CI. The 95% CI is to be calculated using the Miettinen-Nurminen method, available in the FREQ procedure of SAS 9.4.

Population: safety analysis set.

14.1.10. Listings

Listing 16.2.10.1: Treatment-emergent adverse events: Summary listing

Summary listing per treatment group and per subject showing the following:

- Treatment start/stop date(time);
- AE preferred term (flagging ISR of grade 3 or higher and skin related AEs);
- AE start and end date(time);
- AE onset day in study;

- AE number;
- AE duration;
- AE intensity (CTCAE version 5.0);
- AE seriousness;
- AE relatedness to study drug;
- AE action taken;
- AE outcome.

This listing will show all information for each TEAE record fitting in one line. Each change in seriousness/intensity/relationship/action taken will be displayed each time in another line with the AE start date of this change and the AE stop date of this change.

Population: safety analysis set.

Listing 16.2.10.2: Treatment-emergent adverse events: Full listing

Full listing per treatment group and per subject and per analysis period showing the following:

- Treatment start date(time);
- AE system organ class, preferred term, verbatim term;
- AE start and end date(time);
- AE onset day in study;
- AE number;
- AE duration;
- AE intensity (CTCAE version 5.0);
- AE seriousness;
- AESI category (ISR and skin related events);
- AE relatedness to study drug;
- AE outcome;
- AE action taken;
- Concomitant therapy started (yes/no) because of the AE (and the generic name of the medication).

Each change in seriousness/intensity/relationship/action taken will not be displayed but the worst case for each parameter will be provided.

Population: safety analysis set.

Listing 16.2.10.3: Treatment-emergent adverse events: Summary listing of the grade 3 or higher adverse events

Same as Listing 16.2.10.1, only showing grade 3 or higher TEAEs.

Population: safety analysis set.

Listing 16.2.10.4: Treatment-emergent adverse events: Full listing of the grade 3 or higher adverse events

Same as Listing 16.2.10.2, only showing grade 3 or higher TEAEs.

Population: safety analysis set.

Listing 16.2.10.5: Adverse events: Full listing of the serious adverse events

Same as Listing 16.2.10.2, only showing SAEs, whether treatment-emergent or not.

Population: safety analysis set.

Listing 16.2.10.6: Pre-treatment adverse events: Full listing

Same as Listing 16.2.10.2, only showing the AE records reported in the screening period.

Population: safety analysis set.

Listing 16.2.10.7: Adverse events: Summary listing of the injection site reactions events

Same as Listing 16.2.10.1, only showing ISR events.

Population: safety analysis set.

Listing 16.2.10.8: Adverse events: Full listing of the injection site reactions events

Full listing per treatment group, per subject and time point showing the following:

- Treatment start date(time);
- ISR start and end date(time);
- ISR system organ class and preferred term;
- ISR anatomical site;
- ISR grade;
- ISR action taken;
- Narrative;
- Photography taken (yes/no);
- Erythema grade and extent;
- Edema grade and extent;
- Induration extent;
- Tenderness VAS;
- Itching VAS.

Population: safety analysis set.

Listing 16.2.10.9: Adverse events: Summary listing of the skin related adverse events

Same as Listing 16.2.10.1, only showing skin related events.

Population: safety analysis set.

Listing 16.2.10.10: Adverse events: Full listing of the skin related adverse events

Full listing per treatment group, per subject showing the following:

- Treatment start date(time);
- AE start and end date(time);
- AE system organ class and preferred term;
- Photography taken (yes/no and the anatomical site of lesion);
- Skin swab (yes/no and the anatomical site of lesion);
- Biopsy (yes/no and the anatomical site of lesion);
- Additional blood sample for cytokine analysis (yes/no);
- Tests and results (for cytokine analysis);
- Description of results and final diagnosis.

Population: safety analysis set.

Listing 16.2.10.11: Adverse events: Full listing of adverse events with temporarily discontinued as action

Same as Listing 16.2.10.2 only showing AEs, with action taken study drug temporarily discontinued, whether related to study drug or not.

Population: safety analysis set.

Listing 16.2.10.12: Adverse events: Full listing of adverse events with permanently discontinued as action

Same as Listing 16.2.10.2 only showing AEs, with action taken study drug permanently discontinued, whether related to study drug or not.

Population: safety analysis set.

Listing 16.2.10.13: Adverse events: Coding information

Overview listing of all distinct MedDRA coding pathways for all AEs reported in this study and population, from AE reported term until AE system organ class, also showing the subjects associated to each distinct coding pathway.

Population: safety analysis set.

14.2. NON-DRUG RELATED THERAPIES

14.2.1. Coding of Reported Terms

All therapies are expected to be coded using the MedDRA coding dictionary (version 21.0 or higher).

14.2.2. Calculation of the Relative Days

For both the start and the end dates of the therapy records, their day relative to the day of the first study drug administration will be calculated as described in section 5.4 of this SAP (calculation of relative days).

The relative day for a missing start date will be set to missing.

The relative day for an incomplete start or end date will be set to missing.

The relative day for a missing end date will be calculated up to the subject's date of last contact in study, and will be printed as '>X days'.

14.2.3. Analysis

Table 14.3.1.20: Non-drug related therapies

Number (percent) of subjects per treatment group classified per system organ class and preferred term.

Population: safety analysis set.

Listing 16.2.10.14: Non-drug related therapies

Listing per treatment group and per subject of all non-drug therapy records.

When these records are linked to medical history or adverse events, these additional details (reported term of the medical history condition(s) or reported term of the adverse event(s), including their record ID numbers) will be printed as well.

Population: safety analysis set.

14.3. LABORATORY SAFETY

14.3.1. Available Data

Laboratory parameters expected are described in the protocol (section 6.5.2 of the protocol). Only central laboratory data will be included.

14.3.2. Number of Significant Digits

The standardized results of continuous laboratory parameters, as well as their standardized normal limits, will be mapped to analysis values and analysis normal limits without rounding.

Only for printing in the analysis TLFs, a maximum of 3 decimal positions will be shown.

14.3.3. Categorization of Laboratory Parameters

Laboratory parameters will be presented grouped into three main categories: biochemistry, hematology and coagulation. Urinalysis, serology, cytokines and pregnancy test will be only listed. All central lab data will be listed even unscheduled lab category/parameter.

14.3.4. Derivation of Laboratory Parameters

NAP.

14.3.5. Baseline and Change from Baseline

The baseline is defined as the last sample prior to the first dose of study medication. Baseline will be determined per lab test individually. It is recognized that baseline tests may thus come from more than one lab sample and not just from the “baseline visit” sample.

The change from baseline will be calculated for all post-baseline time points as:

Change from baseline at time point t = value at time point t – baseline value.

14.3.6. Scoring of Laboratory Values

14.3.6.1. Scoring According to Normal Ranges

The position of the actual analysis values versus their normal ranges will be determined directly using the position indicator provided in the database as reported by the laboratory (lbnrind), expressing the classes for these analysis values as low (L), normal (N) or high (H).

14.3.6.2. According to CTCAE Grades

CTCAE version 4.03 classification is only for the below tests. For other tests, only the classification according to normal ranges will be done.

Chemistry:

Laboratory test	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Albumin (g/L)	≥ LLN	[30,LLN[	[20,30[	<20	(NAP)
ALT (U/L)	≤ ULN	]1.0,3.0] x ULN	]3.0,5.0] x ULN	]5.0,20.0] x ULN	> 20.0 x ULN
AST (U/L)	≤ ULN	]1.0,3.0] x ULN	]3.0,5.0] x ULN	]5.0,20.0] x ULN	> 20.0 x ULN
Alkaline phosphatase (U/L)	≤ ULN	]1.0,2.5] x ULN	]2.5,5.0] x ULN	]5.0,20.0] x ULN	> 20.0 x ULN
GGT (U/L)	≤ ULN	]1.0,2.5] x ULN	]2.5,5.0] x ULN	]5.0,20.0] x ULN	> 20.0 x ULN
Total bilirubin (µmol/L)	≤ ULN	]1.0,1.5] x ULN	]1.5,3.0] x ULN	]3.0,10.0] x ULN	> 10.0 x ULN
Calcium low (mmol/L)	≥ LLN	[2.00,LLN[	[1.75,2.00[	[1.50,1.75[	<1.50
Calcium high (mmol/L)	≤ ULN	]ULN,2.9]	]2.9,3.1]	]3.1,3.4]	>3.4
Total cholesterol (mmol/L)	≤ ULN	]ULN,7.75]	]7.75,10.34]	]10.34,12.92]	>12.92
Creatinine (µmol/L)	≤ ULN	]1.0,1.5] x ULN	]1.5,3.0] x ULN	]3.0,6.0] x ULN	> 6.0 x ULN
Creatinine kinase	≤ ULN	]1.0,2.5] x ULN	]2.5,5.0] x ULN	]5.0,10.0] x ULN	> 10.0 x ULN
Glucose low (mmol/L)	≥ LLN	[3.0,LLN[	[2.2,3.0[	[1.7,2.2[	<1.7
Glucose high (mmol/L) [fasting]	≤ ULN	]ULN,8.9]	]8.9,13.9]	]13.9,27.8]	>27.8
Phosphate (mmol/L)	≥ LLN	[0.8,LLN[	[0.6,0.8[	[0.3,0.6[	<0.3
Potassium low (mmol/L)	≥ LLN	[3.0,LLN[	(NAP)	[2.5,3.0[	<2.5
Potassium high (mmol/L)	≤ ULN	]ULN,5.5]	]5.5,6.0]	]6.0,7.0]	>7.0
Sodium low (mmol/L)	≥ LLN	[130,LLN[	(NAP)	[120,130[	<120
Sodium high (mmol/L)	≤ ULN	]ULN,150]	]150,155]	]155,160]	>160
Triglycerides (mmol/L)	< 1.71	[1.71,3.42]	]3.42,5.7]	]5.7,11.4]	> 11.4

Hematology:

Laboratory test	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (g/L)	≥ LLN	[100,LLN[	[80,100[	< 80	(NAP)
WBC (giga/L)	≥ LLN	[3.0,LLN[	[2.0,3.0[	[1.0,2.0[	<1.0
Lymphocyte count decreased (giga/L)	≥ LLN	[0.8,LLN[	[0.5,0.8[	[0.2,0.5[	< 0.2
Lymphocyte count increased (giga/L)	(NAP)	(NAP)	]4,20]	>20	(NAP)
Neutrophils (giga/L)	≥ LLN	[1.5,LLN[	[1.0,1.5[	[0.5,1.0[	< 0.5
Platelet count (giga/L)	≥ LLN	[75,LLN[	[50,75[	[25,50[	< 25

Coagulation:

Laboratory test	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Activated Partial thromboplastin time (s)	≤ ULN	]1.0,1.5] x ULN	]1.5,2.5] x ULN	> 2.5 x ULN	(NAP)
INR	≤ ULN	]1.0,1.5] x ULN	]1.5,**2.5**] x ULN	> **2.5** x ULN	(NAP)
Laboratory test	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Activated Partial thromboplastin time (s)	≤ ULN	]1.0,1.5] x ULN	]1.5,2.5] x ULN	> 2.5 x ULN	(NAP)

Note:

- LLN = lower normal limit,
- ULN = upper normal limit,
- (NAP) = grade does not exist.

14.3.7. Treatment-emergent Principle

14.3.7.1. Toxicity Grades

A post-baseline toxicity grade 1, 2, 3 or 4 is defined as treatment-emergent when higher than the toxicity grade of the baseline result. If the baseline result is missing, a post-baseline toxicity grade 1, 2, 3 or 4 will always be considered as treatment-emergent.

14.3.7.2. Non-graded Abnormalities

A post-baseline non-graded abnormality class L or H is defined as treatment-emergent when it differs from the abnormality class of the baseline result. If the baseline result is missing, a post-baseline abnormality L or H will always be considered as treatment-emergent.

14.3.8. Determination of Worst-case Abnormality

14.3.8.1. According to Normal Range

The worst-case post-baseline result position versus normal range (L/N/H) will be determined per subject and per parameter.

The following worst-cases will be determined, using all non-missing post-baseline records (including unscheduled and follow-up visits):

- H = high:
  At least one post-baseline result is classified as H, and there are no results classified as L.
- L = low:
  At least one post-baseline result is classified as L, and there are no results classified as H.
- H+L = high and low:
  At least one post-baseline result is classified as H, and at least another post-baseline result is classified as L.
- N = normal: All post-baseline results are classified as N.

14.3.8.2. According to CTCAE Grades

The worst-case post-baseline toxicity grade 0, 1, 2, 3 or 4 will be determined per subject and per parameter (and direction, if below and above), using all non-missing post-baseline records (including unscheduled and follow-up visits).

14.3.9. Handling of Categorical Laboratory Parameters

Categorical laboratory parameters (usually urinalysis) will only be listed. No determination of toxicity grades nor determination of worst-cases apply to these parameters.

14.3.10. Tables

Laboratory parameters with an overall low sample size (<2 observations looking at the whole study) will not be presented in tables, but only in listings.

All tables in this section will be presented per treatment group and analysis visit/time point.

Table 14.3.2.1: Laboratory data: Descriptive statistics of the actual values and change from baseline per time point

Descriptive statistics of the actual values and changes from baseline (including 95% CI of the mean for change from baseline values) per laboratory test category, parameter, treatment group and analysis visit/time point.

Population: safety analysis set.

Table 14.3.2.2: Laboratory data: Worst-case shift table according to the normal range

Shift table per laboratory test category, parameter and treatment group.

This table will present the shift in abnormality (L/N/H) for the worst-case versus the baseline abnormality (L/N/H).

Table for lab tests with normal ranges.

Population: safety analysis set.

Table 14.3.2.3: Laboratory data: Worst-case treatment-emergent laboratory abnormalities

Frequency table of the worst-case treatment-emergent abnormalities per laboratory test category, parameter and treatment group.

Table for lab tests with normal ranges.

Population: safety analysis set.

Table 14.3.2.4: Laboratory data: Worst-case CTCAE toxicity grades

Frequency table of the worst-case CTCAE toxicity grades (including cumulative percentages) per laboratory test category, laboratory test and treatment group.

Table for lab tests with CTCAE grading.

Population: safety analysis set.

Table 14.3.2.5: Laboratory data: Worst-case shift table of the CTCAE toxicity grades

This table will present the shift in CTCAE toxicity grade for the worst-case versus the CTCAE toxicity grade of the baseline result per laboratory test category, laboratory test and treatment group.

Table for lab tests with CTCAE grading.

Population: safety analysis set.

Table 14.3.2.6: Laboratory data: Worst-case treatment-emergent CTCAE toxicity grades

Frequency table of the worst-case treatment-emergent lab CTCAE toxicity grades per lab test category, lab test and treatment group.

Table for lab tests with CTCAE grading.

Population: safety analysis set.

14.3.11. Figures

Figure 14.3.2.1: Laboratory data: Mean (+/- SE) of the actual values over time

Arithmetic mean with SE of the laboratory test results over time, with both treatment groups on the same plot (all study days/time points to be displayed on the same plot). Each laboratory parameter will be on a new plot.

Population: safety analysis set.

Figure 14.3.2.2: Laboratory data: Mean (+/- SE) of the changes from baseline over time

Arithmetic mean with SE of the laboratory test change from baseline results over time, with both treatment groups on the same plot (all study days/time points to be displayed on the same plot). Each laboratory parameter will be on a new plot.

Population: safety analysis set.

14.3.12. Listings

Next to the actual values and the changes from baseline, all listings will present the following parameters:

- The sample date and time;
- The subject's fasting status for the laboratory sample (Y or N);
- The value abnormality (result position versus normal range, L or H);
- The CTCAE toxicity grade (where applicable)
- The normal range associated to the parameter value;
- Any related comments.

Listing 16.2.11.1: Laboratory data: Full listing

Listing per treatment group, per subject, parameter and analysis visit/time point of all data.

Population: safety analysis set.

Listing 16.2.11.2: Laboratory data: Listing of treatment-emergent abnormalities

Listing per treatment group, per subject and per time point of all post-baseline time points scored as treatment-emergent (normal ranges and toxicity grades), plus also the baseline reference time point.

Population: safety analysis set.

14.4. ECG

14.4.1. Available Data

The following provided ECG parameters will be analyzed: heart rate, RR interval, PR interval, QRS interval, uncorrected QT interval, QT interval corrected for the heart rate using Fridericia's formula (QTcF) and QT interval corrected for the heart rate using Bazett's formula (QTcB).

14.4.2. Number of Significant Digits

The standardized results of continuous ECG parameters will be mapped to analysis values without rounding.

Only for printing in the analysis TLFs, a maximum of 3 decimal positions will be shown.

14.4.3. Derivation of ECG Parameters

No derivation of ECG parameters will be done. Data as recorded in the CRF/external ECG vendor file will be used for analyses.

14.4.4. Handling of ECGs Measured in Triplicate

The mean over the triplet will be calculated for each parameter. Mean values will be derived during the statistical analysis. Only means will be reported in tables and listings.

14.4.5. Definition of Normal Ranges and Abnormalities

For the QT, QTcF and QTcB parameters, the following categorizations will be done:

- of the actual values:
  - <= 450 ms (considered as normal range),
  -]450,480] ms,
  -]480,500] ms,
  - >500 ms;
- of the changes from baseline:
  - <= 30 ms (including all decreases in QT) (considered as normal range),
  -]30,60] ms,
  - >60 ms.

For PR, the following categorizations will be done:

- < 120 ms,
- [120, 220] ms (considered as normal range),
- >220 ms;

For heart rate, the following categorizations will be done:

- < 50 bpm,
- [50, 100] bpm (considered as normal range),
- >100 bpm;

14.4.6. Definition of Treatment-emergent ECG Abnormalities

Actual value: An abnormal post-baseline abnormality is defined as treatment-emergent when the abnormality is worse compared to the abnormality at baseline. When the baseline value is missing, post-baseline abnormalities are always considered as treatment-emergent.

An abnormal category for change from baseline is always treatment-emergent.

14.4.1. Determination of Worst-case Abnormality

The worst-case post-baseline categorized actual analysis value and the worst-case categorized change from baseline will be determined per subject and per parameter, using all non-missing post-baseline records (including unscheduled and follow-up visits).

The worst-case categorized actual analysis value is the category corresponding to the highest post-baseline actual value.

The worst-case change from baseline is the category corresponding to the largest increase (positive change) from baseline.

14.4.2. Tables

Table 14.3.3.1: ECG: Descriptive statistics of the actual values and change from baseline per time point

Descriptive statistics of the actual values and changes from baseline (including 95% CI of the mean for change from baseline values) per parameter, treatment group and analysis visit/time point.

Population: safety analysis set.

Table 14.3.3.2: ECG: Worst-case shift table of the categorized actual values

This table will present the shift in categorized actual values for the worst-case versus the categorized baseline value per parameter (QT, QTcF, QTcB, PR and HR) and treatment group.

Population: safety analysis set.

Table 14.3.3.3: ECG: Worst-case treatment-emergent categorized QT and QTc actual value abnormalities

Frequency table of the treatment-emergent categorized abnormal actual values per parameter (QT, QTcF and QTcB), treatment group for the worst-case.

Population: safety analysis set.

Table 14.3.3.4: ECG: Worst case treatment-emergent HR and PR actual values abnormalities

Frequency table of the treatment-emergent categorized (L, N, H) abnormal actual values per parameter (PR and HR), treatment group for the worst-case.

Population: safety analysis set.

Table 14.3.3.5: ECG: Worst-case treatment-emergent categorized abnormal changes from baseline in QT and QTc

Frequency table of the worst-case treatment-emergent categorized abnormal changes from baseline per parameter (QT, QTcF and QTcB) and treatment group.

Population: safety analysis set.

Table 14.3.3.6: ECG: Frequency table of the eCRF ECG interpretation per time point

Frequency table per treatment group and time point of the ECG interpretation scores. Interpretation scores are: Normal/Abnormal.

Population: safety analysis set.

14.4.3. Listings

Next to the actual values and the changes from baseline, all listings will present the following parameters:

- The abnormality of the actual values and of changes from baseline;
- Any input related interpretations of the ECG;
- Any related comments.

Listing 16.2.12.1: ECG: Full listing

Listing per treatment group, per subject, parameter and analysis visit/time point of all data.

Population: safety analysis set.

Listing 16.2.12.2: ECG: Listing of treatment-emergent abnormalities

Listing per treatment, subject, parameter and analysis visit/time point showing only analysis visits/time points having treatment-emergent abnormal results (on actual value and/or on changes from baseline). Next to the selected analysis visits/time points, the baseline record will fully be presented at all times.

Population: safety analysis set.

14.5. VITAL SIGNS

14.5.1. Available Data

The following provided vital signs parameters will be analyzed: weight, heart rate, diastolic and systolic blood pressure and temperature.

14.5.2. Number of Significant Digits

The standardized results of continuous vital signs parameters will be mapped to analysis values without rounding.

Only for printing in the analysis TLFs, a maximum of 3 decimal positions will be shown.

14.5.3. Derivation of Vital Signs Parameters

NAP.

14.5.4. Definition of Normal Ranges and of Abnormalities

The actual analysis values for the following vital signs parameters will be categorized into abnormality classes according to their position to normal range (table below), defining these classes as low (L), normal (N) or high (H).

Values within or equal to the normal range boundaries are considered normal (N). Values below the lower limit of the normal range are categorized as low (L), and values above the upper limit of normal range are categorized as high (H).

Parameter (unit)	**Normal range**	
	Lower limit	**Upper limit**
Heart rate (bpm)	40	100
DBP (mmHg)	45	90
SBP (mmHg)	90	140
Temperature (°C)	35.5	37.5

14.5.5. Definition of Treatment-emergent Vital Signs Abnormalities

A post-baseline abnormality class L or H is defined as treatment-emergent when it differs from the abnormality class at baseline. If the baseline result is missing, a post-baseline abnormality L or H will always be considered as treatment-emergent.

14.5.6. Determination of the Worst-case Abnormality

The following worst-case post-baseline abnormalities L, N or H will be determined per subject and per parameter, using all non-missing post-baseline records (including unscheduled and follow-up visits):

- H = high:
  At least one post-baseline result is classified as H, and there are no results classified as L.
- L = low:
  At least one post-baseline result is classified as L, and there are no results classified as H.
- H+L = high and low:
  At least one post-baseline result is classified as H, and at least another post-baseline result is classified as L.
- N = normal: All post-baseline results are classified as N.

14.5.7. Tables

Table 14.3.4.1: Vital signs: Descriptive statistics of the actual values and change from baseline per time point

Descriptive statistics of the actual values and changes from baseline (including 95% CI of the mean for change from baseline values) per parameter, treatment group and analysis visit/time point.

Table 14.3.4.2: Vital signs: Worst-case shift table according to the normal range

This table will present the shift in abnormality (L/N/H) for the worst-case versus the baseline abnormality (L/N/H) per parameter and treatment group. Parameters without normal ranges will not be presented.

Population: safety analysis set.

Table 14.3.4.3: Vital signs: Worst-case treatment-emergent abnormalities

Frequency table of the treatment-emergent abnormalities per parameter, treatment group for the worst-case. Parameters without normal ranges will not be presented.

Population: safety analysis set.

14.5.8. Listings

Next to the actual values and the changes from baseline, all listings will present the following parameters:

- The value abnormality (result position versus normal range, L or H);
- The normal range associated to the parameter value;
- Position in which the measurement was taken (sitting, standing or supine).

Listing 16.2.13.1: Vital signs: Full listing

Listing per treatment group, per subject, parameter and analysis visit/time point of all data.

Population: safety analysis set.

Listing 16.2.13.2: Vital signs: Listing of treatment-emergent abnormalities

Listing per treatment, subject, parameter and analysis visit/time point showing only analysis visits/time points having treatment-emergent results. Next to the selected analysis visits/time points, the baseline record will fully be presented at all times.

Population: safety analysis set.

14.6. PHYSICAL EXAMINATIONS

Listing 16.2.14.1: Physical examinations: Abnormalities

Listing per treatment group, per subject and per analysis visit/time point only showing the visits having abnormal physical examination findings.

Population: safety analysis set.

15. REFERENCES

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16. APPENDIX

16.1. PK DATA REVIEW

For the review of PK/ data, following items should be checked:

I. PK
- I.1. MISSING PK DATA
  - I.1.1. Missing concentrations/measurement
- I.2. REVIEW OF PK PROFILES AND CONCENTRATION VALUES
  - I.2.1. Abnormal PK concentration/measurement profiles
  - I.2.2. Abnormal PK concentration/measurement data point
- II. PK ANALYSIS SET

II. PK ANALYSIS SET