STATISTICAL ANALYSIS PLAN

1297.9

PHARMACOKINETICS, SAFETY, IMMUNOGENICITY AND EFFICACY OF BI 695501 VERSUS HUMIRA® IN PATIENTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS: A RANDOMIZED, DOUBLE-BLIND, PARALLEL-ARM, MULTIPLE-DOSE, ACTIVE COMPARATOR TRIAL

AUTHOR:

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE 1/2

Statistical Analysis Plan V2.1 (Dated 03 September 2019) for Protocol version 1297.9 version 3.0.

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE 2/2

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OUTPUT TEMPLATES SIGNATURE PAGE

Please refer to Output Templates V2.0 (Dated 02AUG2019) for Protocol 1297.9.

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2.0	02 August 2019		Adaptation of primary endpoint analysis strategy Deletion of primary analysis after the last patient has completed their Week 32 assessment.
2.1	03 September 2019		Update of Appendix 7 - Laboratory Assessments

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ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
anti-HBc	Anti-hepatitis B core antibodies
anti-HCV	Hepatitis C antibodies
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Boehringer Ingelheim
BLQ	Below the limit of quantitation
CI	Confidence interval
Cmax	Maximum concentration of the analyte in plasma
Cmin	Minimum concentration of the analyte in plasma
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Coefficient of variation
DB	Double-Blind
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EoT	End-of-Treatment
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
IGRA	Interferon gamma-release assay
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
nAb	Neutralizing antibody
NOA	Not analysed
NOP	No Peak
NOR	No valide result

NOS	No sample
NRI	Non-responder imputation
PASI	Psoriasis Area and Severity Index
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Set
PPD	Purified protein derivative
PPS	Per-Protocol Analysis Set
RA	Rheumatoid arthritis
RI	Run-in
RTS	Run-in Treated Set
TS	Treated Set
SAE	Serious adverse event
SFU	Safety Follow-up
SOP	Standard operating procedure
SPC	Summary of product characteristics
sPGA	Static Physician's Global Assessment
TB	Tuberculosis
Tmax	Time to reach maximum concentration
ULN	Upper limit of normal
US	United States
WHO	World Health Organisation

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of pharmacokinetics (PK) safety, immunogenicity and efficacy data for Protocol 1297.9. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 3.0, dated 25th July 2019.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this trial is to assess the PK similarity between patients receiving United States (US)-licensed Humira® continuously vs those who switch between BI 695501 and US-licensed Humira®, in patients with moderate to severe chronic plaque psoriasis.

2.2. SECONDARY OBJECTIVES

The secondary objectives of this trial are to descriptively compare the:

- safety,
- immunogenicity, and
- efficacy

profiles between patients receiving US-licensed Humira® continuously vs those who switch between BI 695501 and US-licensed Humira®.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a 58-week, multiple-dose, active comparator trial with a single-arm run-in period of 14 weeks duration for all entered subjects, followed by a randomized, double-blind, two-arm period of 34 weeks. The total treatment period will be 48 weeks followed by 10 weeks of safety follow-up.

All entered subjects will have a planned run-in period of 14 weeks during which they will be treated with US-licensed Humira®. Approximately 240 subjects will be entered into the run-in US-licensed Humira® arm.

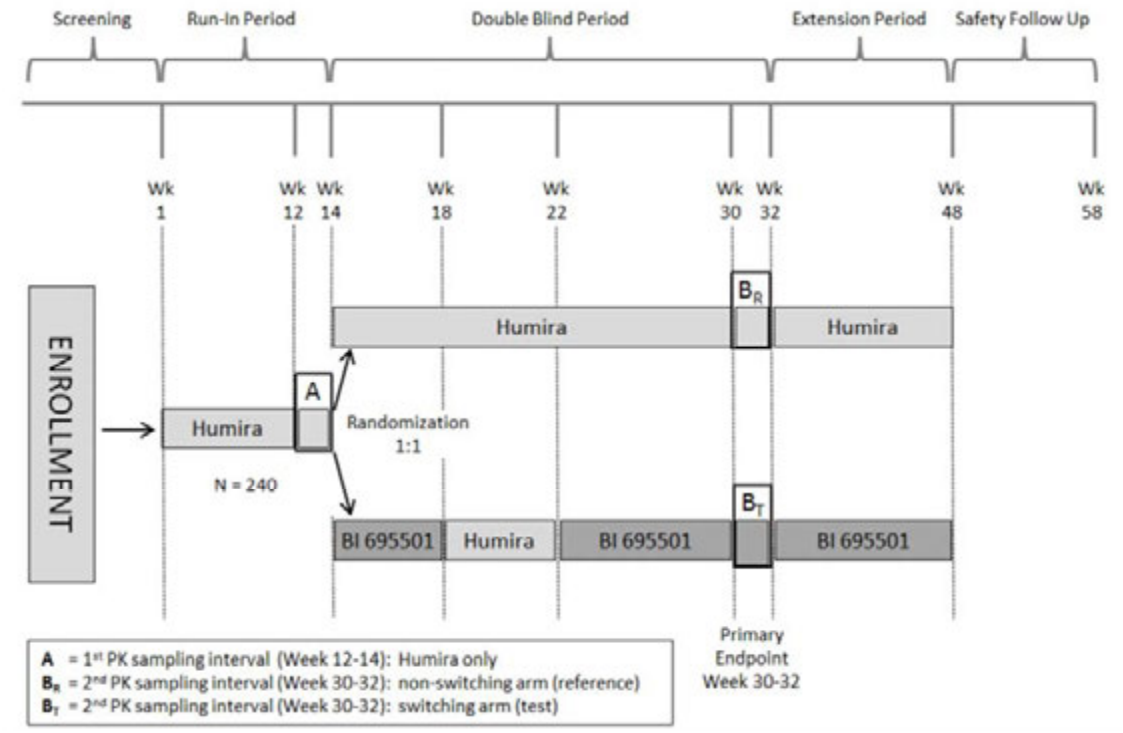
At the beginning of Week 14 (Day 92), subjects achieving at least a 50% reduction in Psoriasis Area and Severity

Index (PASI50) response will be randomized in a 1:1 ratio to either continue receiving US-licensed Humira® (continuous US-licensed Humira® arm) until Week 48 or receive BI 695501/US-licensed Humira®/BI 695501 alternately for three periods (switching arm) in a blinded fashion. The randomization will be stratified by the level of their Week 14 response (PASI50 to <PASI75 or ≥ PASI75). In the switching arm, the first two periods of switching will be of 4 weeks (2 injections) duration, and the third treatment period will be of 10 weeks (5 injections) duration, with an extension period of 16 weeks beyond the Week 32. All subjects will continue to receive 40 mg US-licensed Humira® or BI 695501 every other week until the end of the treatment period (Week 48).

Those subjects not achieving at least PASI50 at Week 14 will be discontinued from any further treatment in the study, but will undergo the End-of-Treatment (EoT) and Safety Follow-Up (SFU) for safety.

Subjects will undergo intensive PK sampling between Weeks 12-14 (Days 78-92), and Weeks 30-32 (Days 204-218) to assess PK similarity between the two arms.

Table A: Trial Design



3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section "FLOW CHART" of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

No change from protocol.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Blinded review of sample size (after approximately 86 subjects have the Week 32 endpoints assessment and are PK evaluable)
- Final Analysis (after Database lock, based on all available data)

This document will provide details for Blinded review of sample size and Final Analysis.

The analysis described in the TSAP will be performed by Biostatistics following Sponsor Authorization of the Statistical Plan, Sponsor Authorization of Analysis Sets and Data Snapshot/Database Lock.

4.1. BLINDED REVIEW OF SAMPLE SIZE

The Blinded review of sample size will be performed when the two primary endpoints, PK parameters $AUC_{\tau, 30\text{-}32}$ and $C_{max, 30\text{-}32,}$ are available for approximately 86 PK evaluable subjects (cf. definition of PKS in Section 5.5). The analysis will be done on verified data, no open queries reside on the data used for the analysis.

The PK parameterswill be determined by BI in a blinded fashion and then send to for analysis. This analysis will be performed by a blinded statistician in order to evaluate the variability to assess whether the initially planned sample size will be increased or not; this analysis will also include descriptive statistics for $AUC_{\tau, 30\text{-}32}$ and $C_{max, 30\text{-}32}$, $AUC_{\tau, 12\text{-}14}$ and $C_{max, 12\text{-}14}$. If the new calculated sample size is lower than the initial one, the initially planned sample size will be kept, i.e., 240 subjects to obtain approximatively 170 PK evaluable subjects. A maximum sample size to be recruited is set to 350 subjects to obtain approximatively 246 PK evaluable subjects.

Regarding the difference between the number of enrolled subjects and the number of PK evaluable subjects, it is assumed that approximately 80% of subjects achieve PASI50 at Week 14 (and thus will be randomized into the double blind trial part) and that the PK non-evaluable drop-out rate is about 10% to 15%, leading to an overall drop-out rate of approximately 30%.

5. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the

unblinding for Final analysis. For the BSSR this will bedone at the data base snapshot date.

5.1. ALL SUBJECTS ENROLLED SET [ENR]

The all subjects enrolled (ENR) set will contain all subjects who provide informed consent for this trial.

5.2. RUN-IN TREATED SET [RTS]

The Run-in Treated Set (RTS) will contain all subjects in the ENR set treated with at least one dose of Humira® during the run-in period.

If there is any doubt whether a subject was treated or not, the subject will be assumed treated for the purposes of analysis.

5.3. ALL SUBJECTS RANDOMIZED SET [RND]

The all subjects randomized (RND) set will contain all subjects in the ENR set who were randomized to trial medication.

For analyses and displays based on RND, subjects will be classified according to randomized treatment.

5.4. TREATED SET [TS]

The Treated Set (TS) will contain all subjects in the RND set treated with at least one dose of trial medication administered in the randomized phase.

If there is any doubt whether a subject was treated or not, the subject will be assumed treated for the purposes of analysis.

For analyses and displays based on TS:

- In case the subject was fully incorrectly treated, the subject will be classified according to treatment received
- In case the subject was partially incorrectly treated, the subject will be classified according to treatment randomized.

Fully incorrectly treated: Subject who received the wrong treatment at each visit from W14 to W48.

Partially incorrectly treated: Subject who received at least once the wrong treatment and at least once the good one from W14 to W48. A listing of AEs for partially incorrect treated subjects will be performed.

5.5. PHARMACOKINETIC SET [PKS]

The Pharmacokinetic Set (PKS) includes all patients from the Treated Set (TS) who provide at least one primary PK parameter that was not excluded due to a protocol violation relevant to the evaluation of PK according to the description below.

- Deviations from visit windows

Visit windows in the CTP were defined for operative reasons. If deviations from these windows will lead to exclusion from analysis of PK endpoints will be assessed and decided no later than the blinded Data Review Meeting.

Relevant protocol violations within the time period critical for primary endpoint evaluation (i.e., from Baseline to W32-Visit 18) may be:

- Incorrect trial medication taken, i.e., the subject received at least one dose of trial medication the subject was not assigned to

If a patient took the medication he/she was not assigned to (e.g. received Humira when BI 695501 was scheduled or vice versa) during the study until including visit 17, PK parameters after incorrect intake of trial medication will be excluded from statistical analysis.

- Incomplete dose of trial medication taken

For incomplete dose of trial medication the same rules as for missed doses will be applied.

- Missed doses of trial medication

A delay of dose by 7 days or more (resulting in a dosing interval length of 21 days or longer) will be considered as a missed dose.

- Missed doses during run-in phase (until including visit 8)

If one dose until including visit 6 was missed, PK parameters of dosing interval week 12-14 (intensive PK interval run-in phase) will be included in the statistical analysis.

If more than one dose was missed until including visit 8, PK parameters of intensive PK interval in run-in phase will be excluded from statistical analysis.

If dose at visit 7 was missed, PK parameters of intensive PK interval in run-in phase will be excluded from statistical analysis.

If dose at visit 8 was missed, PK parameters of intensive PK interval in run-in phase will not be calculated.

- Missed doses during randomized phase

If one dose from including visit 9 until including visit 15 was missed, PK parameters will be included in the statistical analysis.

If more than one dose was missed until including visit 17, PK parameters of dosing interval week 30-32 (intensive PK interval in randomized phase) will be excluded from statistical analysis.

If dose at visit 16 was missed, PK parameters of intensive PK interval in randomized phase will be excluded from statistical analysis.

If dose at visit 17 was missed, PK parameters of intensive PK inteval in randomized phase will not be calculated.

If doses are missed from including visit 18 until end of the study, PK parameters will be included in the statistical analysis.

- Use of restricted medications with suspected impact on PK

If Methotrexate was used once or repeatedly within 7 days prior to visit 2 or during the study until including visit 18, PK parameters will be excluded from statistical analysis.

If Methotrexate was used after visit 18 (week 32), PK parameters will be included in the statistical analysis.

- Missed plasma samples during the dosing interval from Week 12 to Week 14 or from Week 30 to 32

If two consecutive samples during visits 8a-d or 17a-d are missing, AUCτ and Cmax of the affected intensive PK interval will not be calculated.

If pre-dose samples at visit 8 and/or 9 are missing, AUCτ,12-14 will not be calculated..

If pre-dose samples at visit 17 and/or 18 are missing, AUCτ,30-32 will not be calculated.

- Missing drug administration or missing PK sampling date or time

Rules below will be applied for missing drug administration or missing PK sampling date and time if missing data could not be imputed (see Section 7.3).

- Missing drug administration date or time of visit 8 or 17

If dosing date or time of visit 8 or 17 is missing, PK parameters of the affected intensive PK interval will not be calculated.

- Missing drug administration date or time of visit 9 or 18

If dosing date or time of visit 9 or 18 is missing, AUCτ of the affected intensive PK interval will not be calculated.

- Missing drug administration date or time (all visits except visit 8, 9, 17 and 18)

If dosing date or time is missing for any other visit except visits 8, 9, 17 and 18, PK parameters will be calculated and included in the statistical analysis.

- Missing PK sampling date or time

Visits 8, 9, 17, or 18:

If PK sampling date or time of visit 8 or 17 is missing, PK parameters of the affected intensive PK interval will not be calculated.

If PK sampling date or time of visit 9 or 18 is missing, AUCτ of affected intensive PK interval will not be calculated.

Visits 2, 3, 6, 11, 13, 22, 27 and 28:

If PK sampling date or time for PK samples is missing for visits 2, 3, 6, 11, 13, 22, 27 and 28, PK parameters will be calculated and included in statistical analysis.

- Deviations from PK sampling times

PK sampling windows in the CTP were defined for operative reasons. Deviations will not necessarily lead to exclusion from analyis of PK endpoints.

Whether a protocol violation is considered relevant for the assessment of PK will be decided no later than in the blinded Data Review Meeting prior to the data snapshot. Exclusion of a patient's data will be documented in the CTR.

For analyses and displays based on PKS, subjects will be classified according to treatment received.

5.6. PER-PROTOCOL ANALYSIS SET [PPS]

The Per-Protocol Analysis Set (PPS) will contain all subjects in the TS who did not experience any important protocol violations relevant for efficacy. Important protocol violations will be reviewed and approved prior to the Data Snapshot/Database Lock. However, additional unexpected protocol deviations may be added afterwards, for violations that can only be assessed with unblinded data (i.e. incorrect treatment medication taken). The important protocol violations relevant for efficacy until Week 32 inclusive may include but are not limited to:

- Incorrect trial medication taken, i.e., at least one kit number used and recorded on the eCRF before Week 32 does not correspond to the randomized treatment group.
- Severe violation of treatment compliance prior to Week 32: medical team will review subjects with treatment compliance strictly below 80% and strictly above 120% (refer to Section 14.1) and decide if the violation is severe.

- Severe violation of inclusion/exclusion criteria
    - Exclusion criterion 2: Prior exposure to any biologic therapies for any auto-immune diseases (e.g.,: RA, Psoriasis, and Crohn's disease).
    - Exclusion criterion 6: Subjects who must or wish to continue the intake of restricted medications (see CTP Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
    - Exclusion criterion 7: Currently enrolled in another investigational device or drug trial, or less than 30 days (or less than 5 half-lives, whichever is longer) since ending another investigational device or drug trial(s), or receiving other investigational treatment(s).
    - Exclusion criterion 10: Forms of psoriasis (e.g., pustular, erythrodermic and guttate) other than chronic plaque psoriasis. Drug-induced psoriasis (i.e., new onset or current exacerbation from e.g., beta-blockers or lithium).
- Severe violations related to inclusion/exclusion criteria will be defined considering the eCRF page displaying the inclusion and exclusion criteria as well as available data in the database at baseline.

A listing of each patient with the information included/excluded from the PPS and the reasons will be provided to BI. Then a Blinded Set Review Meeting will be done between BI and to discuss and confirm which subjects are to be excluded from the PPS. This meeting could be done at the same time as the Data Review Meeting.

Important protocol violations will be defined before unblinding for Final analysis.

For analyses and displays based on PPS, subjects will be classified according to randomized treatment.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

Two reference start dates are defined:

- Reference Run-in Start Date: this reference start date is defined as the day of the first dose of Humira® (Day 1 is the day of the first dose of Humira®).
- Reference Double-Blind Start Date: this reference start date is defined as the day of the first dose of treatment after randomization (planned day is Day 92).

The two reference start dates will appear in every listing where an assessment date or event date appears.

The Study Day is calculated as follows:

- If the date of the event is on or after the reference start date then:

Study Day = (date of event – reference start date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in APPENDIX 2.

6.2. BASELINE

Baseline is defined as the last non-missing measurement taken prior to the Reference date: Reference Run-in Start Date (Run-in Baseline) or Reference Double-Blind Start Date (Double-Blind Baseline).

The immunogenicity, laboratory and safety analysis will be performed separately for both defined baselines (Reference Run-in Start Date and Reference Double-Blind Start Date). Otherwise, baseline is defined as the last non-missing measurement taken prior to reference Run-in start date (including unscheduled assessments).

In the case where the last non-missing measurement and the reference date coincide, that measurement will be considered as baseline.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. In the case of a retest, an unscheduled assessment will be created. For laboratory assessments as described in APPENDIX 7, the latest available measurement within 2 days after the planned assessment will be used for by-visit summaries. Unless assigned to a planned visit number, unscheduled measurements will not be included in by-visit summaries except for secondary efficacy endpoints (refer to Section 17.1.1.1) and DILIs (refer to Section 18.1.6.4).

Treatment early termination data will be included in the End-of-Treatment visit in by-visit table summaries and by-visit graphs, according to the protocol.

Listings will include scheduled, unscheduled, and retest data as collected in the eCRF database.

6.4. WINDOWING CONVENTIONS

Unless otherwise specified, visit data as recorded in the database will be used for the analysis. No visit windowing recalculation will be performed for this trial.

6.5. STATISTICAL TESTS

Confirmatory:

Regarding the PK analyses the confidence intervals will be 90.2%.

Descriptive:

Regarding the efficacy analyses the confidence intervals will be 90% and 95%. Regarding the safety analyses the confidence intervals will be 95%. All tests will be two-sided, unless otherwise specified in the description of the analyses.

6.6. COMMON CALCULATIONS

For quantitative measurements:

- Change from baseline will be calculated as: Test Value at Visit X – Baseline Value
- Relative change from baseline (%) will be calculated as: ((Test Value at Visit X – Baseline Value)/ Baseline Value) x 100.

6.7. SOFTWARE VERSION

Analyses provided by will be conducted using SAS version 9.4 or higher. Analyses provided by BI will be using Phoenix WinNonlin Version 6.3 or higher and SAS Version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in Blinded review of sample size and the analyses of PK. For details of their inclusion in the models, see the specific analysis section.

Treatment (switching arm versus continuously Humira® arm) – except for the Blinded review of sample size

Logarithm* of rPASI, where rPASI is the ratio of PASI at Week 14 and PASI at Week 1

Weight at Week 14

Stage (1 for subjects who finished Week 32 prior to the blinded sample size reassessment versus 2 for the other ones) – except for the Blinded review of sample size

$AUC\tau_{,\ 12\text{-}14}$ or $C_{max,\ 12\text{-}14}$

*natural logarithm

7.2. MULTICENTER TRIAL

This trial will be conducted by multiple investigators at multiple centers internationally, approximatively 80 clinical sites across approximatively 9 countries. Randomization will be stratified by the level of their Week 14 PASI response (≥ PASI50 to < PASI75 and ≥ PASI75). No stratification by site was planned because of the small number of subjects to be randomized per site.

7.3. MISSING DATA

Missing PK data will be handled as described in Section 16.2.3 of this analysis plan.

Missing safety data will not be imputed if not mentioned otherwise.

Missing efficacy data will be handled as described in Section 17.1.1 of this analysis plan.

Calculation for a partial date is described in APPENDIX 2.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

This trial has two primary endpoints: $AUC_{\tau,\ 30\text{-}32}$ and $C_{max,\ 30\text{-}32}$. These two endpoints are considered coprimary (i.e., the trial is considered positive if the results for both endpoints are simultaneously positive), therefore no multiplicity-adjustment with respect to the alpha level will be performed.

7.5. ACTIVE-CONTROL STUDIES INTENDED TO SHOW NON-INFERIORITY OR EQUIVALENCE

The primary objective of the trial is to assess the PK similarity between a treatment arm in which patients will be receiving United States (US)-licensed Humira® continuously and a treatment arm where patients will switch multiple times between BI 695501 and US-licensed Humira®. The relevant PK endpoints are: $AUC_{\tau,\ 30\text{-}32}$ and $C_{max,\ 30\text{-}32}$. The statistical description of these analyses is presented in Section 16.2 of this SAP.

7.6. EXAMINATION OF SUBGROUPS

Not applicable.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this trial and therefore the format and content of the summary tables, figures and listings to be provided by Biostatistics and BI.

9. DISPOSITION AND WITHDRAWALS

Disposition and withdrawals will be presented at the Final Analysis.

All subjects who provide informed consent will be accounted for in this trial.

The counts of the analysis sets will be presented:

- All Subject Enrolled Set (ENR)
- All Subjects Randomized Set (RND)
- Run-in Treated Set (RTS)
- Treated Set (TS)
- Pharmacokinetic Analysis Set (PKS)
- Per Protocol Analysis Set (PPS)

The reasons for exclusion from the analysis sets will be listed.

The following subject disposition and withdrawals will be presented for the ENR set:

- Screened
- Rescreened
- Screen failure (defined as withdrawn from trial prior to randomization). The information will be displayed only once for subjects being rescreened and will correspond to the last information available in the eCRF.
- Primary reason for non-inclusion. The information will be displayed only once for subjects being rescreened and will correspond to the last information available in the eCRF.
- Enrolled but not treated by Humira® during run-in period
- Treated by Humira® during run-in period
- Discontinued from treatment during Run-In period strictly before Day 92 (Week 14) , primary reason for

premature discontinuation from treatment during Run-In period strictly before Day 92 (Week 14)

- Randomized
- Randomized but not treated
- Treated by post-randomization treatment
- Completed treatment at Day 330 (Week 48)
- Completed the trial
- Discontinued from post-randomization treatment, primary reason for premature discontinuation from post-randomization treatment (i.e., after Day 92 (Week 14) and strictly before Day 344 (Week 50))
- Discontinued from trial, primary reason for premature discontinuation from trial

The following subject disposition and withdrawals will be presented for the ENR set per site:

- Screened
- Rescreened
- Screen failure (defined as withdrawn from trial prior to randomization). The information will be displayed only once for subjects being rescreened and will correspond to the last information available in the eCRF.
- Enrolled but not treated by Humira® during run-in period
- Treated by Humira® during run-in period
- Treated by post-randomization treatment
- Randomized
- Randomized but not treated
- Completed treatment at Day 330 (Week 48)
- Completed the trial

9.1. IMPORTANT PROTOCOL DEVIATIONS

Protocol violations as defined in Section 5.6 leading to exclusion from the PPS, will be tabulated and listed for the TS.

Protocol violations as defined in Section 5.5 leading to exclusion from the PKS will be tabulated and listed for the TS.

The full protocol deviations log will be attached to the clinical study report.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic characteristics at Run-in Baseline will be reported at Blinded review of sample size for PKS and at Final Analysis for RTS, TS and PKS:

- Age (years) at Informed Consent
- First age category at Informed Consent
  - Adolescent (< 18 years): AGE < 18 – no subject expected
  - Adults (18-64 years): 18<= AGE < 65
  - Adults (65-79 years): 65<= AGE < 80
  - Adults (Over 80 years): 80<= AGE – no subject expected
- Second age category at Informed Consent
  - AGE < 65 years
  - AGE >= 65 years
- Third age category at Informed Consent
  - AGE < 65 years
  - 65 <= AGE < 76
  - 76 <= AGE <80
  - AGE >= 80
- Gender
  - Male
  - Female
- Country
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not reported
  - Unknown
- Race
  - American Indian or Alaska Native
  - Asian

  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Other
- Height at baseline (cm)

The following demographic characteristics will be reported at Run-in Baseline at Final Analysis for RTS and will be reported at Run-in Baseline and Double-Blind Baseline at Blinded review of sample size for PKS and at Final Analysis for RND, TS and PKS:

- Childbearing potential
  - Post-Menopausal
  - Surgically Sterile
  - Childbearing Potential (includes tubal ligation)
- Weight at baseline (kg)
- BMI at baseline (kg/m2)

The following efficacy baseline characteristic will be reported at Run-in Baseline at Final Analysis for RTS and will be reported at Run-in Baseline and Double-Blind Baseline at Blinded review of sample size for PKS and at Final Analysis for TS, PPS and PKS:

- PASI score as collected in the eCRF

The following efficacy baseline characteristics will be reported at Run-in Baseline at Final Analysis for RTS and will be reported at Run-in Baseline and Double-Blind Baseline at Final Analysis for TS and PPS:

- Static Physician's Global Assessment of psoriasis (sPGA) score at baseline

The following other baseline characteristics will be presented at Run-in Baseline at Final Analysis for RTS and will be reported at Run-in Baseline and Double-Blind Baseline at Final Analysis for TS:

- Infection screen (Hepatitis B (HBsAg anti-HBc), hepatitis C (anti-HCV), HIV)
- Chest X-Ray result
- Tuberculosis (TB) test (IGRA or PPD testing)
- Physical examination (general appearance, skin, head, neck, throat, lymph nodes, cardiovascular and neurological systems, thyroid gland, musculoskeletal system/limbs, respiratory tract and abdomen)

- Vital signs at baseline (Body temperature, blood pressure and pulse rate)
- 12-lead-electrocardiogram at baseline:
  - Normal
  - Abnormal, not clinically significant
  - Abnormal, clinically significant
- Proportion of subjects with positive Anti-Drug Antibody (ADAs) result at baseline
- Proportion of neutralizing anti-drug antibodies results at baseline

Accountability for missing data will be displayed in case of any missing entries.

10.1. DERIVATIONS

Conversion factors:

- 1 pound (lbs) = 0.453592 kilograms (kg)
- 1 inch (in) = 2.54 centimeters (cm)
- Fahrenheit degree (°F) = 1.8 x Celsius degree (°C) + 32

(1 °F = -17.22222 °C)

BMI (kg/ m²) = weight (kg)/(height (m)²)

- PASI:

The PASI is a tool that provides a numeric scoring for subjects' overall psoriasis disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected and the severity of erythema, induration, and desquamation over 4 body regions.

To calculate the PASI, the 4 main body areas are assessed: head (h), trunk (t), upper extremities (u) and lower extremities (l). These correspond to 10%, 30%, 20%, and 40% of the total body area, respectively.

The area of psoriatic involvement of these four areas (Ah, At, Au, and Al) is given a numerical value: 0 = no involvement, 1 = < 10%, 2 = 10% to < 30%, 3 = 30% to < 50%, 4 = 50% to < 70%, 5 = 70% to < 90%, and 6 = 90% to 100% involvement.

The signs of severity, erythema (E), induration (I) and desquamation (D) of lesions are assessed using a numeric scale 0-4 where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores are made independently for each of the areas, h, t, u, and l and represent a composite score for each area. An illustration of judging erythema follows: 0 = no erythema, 1 = slight erythema, 2 = moderate erythema, 3 = severe erythema, and 4 = very severe erythema.

The PASI score is calculated according to the following formula:

$$PASI = 0.1(Eh+Ih+Dh)Ah + 0.3(Et+It+Dt)At + 0.2(Eu+Iu+Du)Au + 0.4(El+Il+Dl)Al$$

11. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History information will be presented at Final Analysis for the RTS and TS.

Surgical and Medical History will be coded using MedDRA version 20.0 or higher.

The system organ classes will be sorted by internationally agreed EMA SOC order (refer to APPENDIX 3), preferred terms will be sorted by decreasing frequencies (within system organ class).

Data captured on the "Medical History and Previous surgical procedures" page of the eCRF will be assigned to prior or concomitant.

See APPENDIX 2 for handling of partial dates for medical history, surgeries and procedures; if it is not possible to define a history, surgery or procedure as prior, concomitant, or post-treatment, it will be classified by the worst case; i.e., concomitant.

- Run-in period
  - Prior medical history, surgeries, and procedures:
    - Start date and stop date of medical history, surgeries, and procedures is prior to or at screening date
  - Concomitant medication:
    - Start date of medical history, surgeries, and procedures prior to the date of first dose of randomized medication

AND

- End date of medical history, surgeries, and procedures after the screening date or were ongoing at the date of first dose of randomized medication

- Post-randomization period
    - Concomitant medical history, surgeries, and procedures:
        - Start date of medical history, surgeries, and procedures prior to or on the end of treatment date

AND

        - End date of medical history, surgeries, and procedures on or after the date of first dose of randomized medication or were ongoing at end of treatment date

For rescreened subject the latest Screening information will be considered.

Prior and concomitant surgical and medical history will be presented by SOC (System Organ Class) and PT (Preferred Term) in two separate tables.

12. MEDICATIONS

General considerations

Medications will be presented at Final Analyses for the RTS and TS. They will be coded using the WHO Drug Dictionary version SEP2016 or higher.

No ATC class coding will be performed. The medical terms will be summarized by WHO-DD Preferred Name. The WHO-DD Preferred Name will be sorted by decreasing frequencies.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e., concomitant.

- Run-in period
    - Prior medications:
        - Start date and stop date of medication is prior to date of first dose of trial medication
    - Concomitant medication:
        - Start date of medication prior to randomization (i.e. randomization Visit included)

AND

        - End date of medication on or after the date of first dose of trial medication (start day of run-in period) or were ongoing at randomization Visit

- Post-randomization period
    - Concomitant medication:
        - Start date of medication prior to or on the end of treatment date

AND

        - End date of medication on or after the date of first dose of randomized medication or were ongoing at end of treatment date

13. TRIAL MEDICATION EXPOSURE

Exposure to trial medication will be presented at Final Analysis for the RTS, TS and PKS.

- Run-in period:

The presentation will be on the RTS:

The proportion of subjects treated by Humira® at each Run-in period planned visit (administration on Week 1, Week 2, Week 4, Week 6, Week 8, Week 10 and Week 12) will be presented.

Descriptive statistics of the number of injections of Humira® per subject will be presented.

Number of subjects per categories of duration of exposure to Humira®, patient time (years) per categories of duration of exposure to Humira®, and descriptive statistics for duration of exposure to Humira® will be presented.

Exposure categories: ≥ 1 day, ≥ 2 weeks, ≥ 4 weeks, ≥ 6 weeks, ≥ 8 weeks, ≥ 10 weeks and ≥ 12 weeks.

These analyses will be presented globally and per randomized treatment group (i.e. subjects will be allocated to either not-randomized if they are not randomized at week 14 or to the randomized treatment group if they are randomized at week 14).

- Overall trial period:

The presentation will be on the TS:

The proportion of subjects treated with trial medication (Run-in period Humira® or randomized trial medication) at each planned visit (administration on Week 1, Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 14, Week 16, Week 18, Week 20, Week 22, Week 24, Week 26, Week 28, Week 30, Week 32, Week 34, Week 36,

Week 38, Week 40, Week 42, Week 44, Week 46 and Week 48) will be presented.

Descriptive statistics for the number of trial medication injections per subject during the trial will be presented.

Number of subjects per categories of duration of exposure to trial medication, patient time (years) per categories of duration of exposure to trial medication, and descriptive statistics for duration of exposure to trial medication will be presented.

Exposure categories: ≥ 1 day, ≥ 2 weeks, ≥ 4 weeks, ≥ 6 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥ 16 weeks, ≥ 22 weeks, ≥ 28 weeks, ≥ 34 weeks, ≥ 40 weeks, ≥ 48 weeks.

These analyses will be presented globally and per randomized treatment group (i.e. subjects will be allocated to either not-randomized if they are not randomized at week 14 or to the randomized treatment group if they are randomized at week 14).

13.1. DERIVATIONS

The date of first and last Run-in period Humira® administration and the date of first and last trial post-randomization treatment administration will be taken from the eCRF page "Trial Medication Injection".

Duration of Run-in period Humira® exposure (days) = Date of last Run-in period Humira® injection - Date of first Run-in period Humira® injection + 1.

Duration of Run-in period Humira® exposure (weeks) = Duration of Run-in period Humira® exposure (days) / 7.

Patient Year Run-in period Humira® Exposure (year) = Cumulative duration of Run-in period Humira® exposure in days per subjects / 365.25

Duration of any trial medication exposure (days) = Date of last trial medication injection - Date of first trial medication injection + 1.

Duration of any trial medication exposure (weeks) = Duration of any trial medication exposure (days) / 7.

Patient Year trial medication exposure (year) = cumulative duration of any trial medication exposure in days per subjects / 365.25

14. TRIAL MEDICATION COMPLIANCE

Compliance to trial medication will be presented at Final Analysis for the TS and PKS.

14.1. DERIVATIONS

Compliance with trial medication will be based on the eCRF page “Trial Medication Injection”. An administered injection is considered when the question “Was full dose given” is answered “Yes”.

Compliance will be based on the comparison of actual administered injections and the planned usage. Compliance will include visits until treatment discontinuation.

‘Per visit’ compliance will be calculated as:

Compliance at visit N = Yes if the question “Was full dose given” is answered “Yes”.

No else

‘Overall’ compliance will be calculated as follows:

Overall compliance (%) = (Number of administered injections)*100/Planned number of injections

Where

Planned usage

Trial Period	**Run-in Period**							
Visit N	1	2	3	4	5	6	7	8
Week		1	2	4	6	8	10	12
Number of injections at visit N	0	2	1	1	1	1	1	1
Planned cumulative number of injections in trial	0	2	3	4	5	6	7	8

Trial Period	**Double-Blind Period**								
Visit N	9	10	11	12	13	14	15	16	17
Week	14	16	18	20	22	24	26	28	30
Number of injections at visit N	1	1	1	1	1	1	1	1	1
Planned cumulative number of injections in trial	9	10	11	12	13	14	15	16	17

Trial Period	Extension Period								
Visit N	18	19	20	21	22	23	24	25	26
Week	32	34	36	38	40	42	44	46	48
Number of injections at visit N	1	1	1	1	1	1	1	1	1
Planned cumulative number of injections in trial	18	19	20	21	22	23	24	25	26

15. BLINDED REVIEW OF SAMPLE SIZE

The blinded, pooled $AUC_{\tau, 30\text{-}32}$ or $C_{max, 30\text{-}32}$ will be monitored to verify the sample size assumptions.

Due to the uncertainty about the PK variability, a sample size re-assessment procedure as described in Friede and Kieser [1] and Golkowski et al [2] has been considered for this study. The initially planned total sample size is 170 PK evaluable subjects (i.e., subjects in the PKS and all necessary covariates are available). This is also set to be the minimum sample size for the trial, denoted as N_{min}.

For this study a maximum sample size to be recruited is set to 350. Taking into account the drop-out rates as described above this translates to a maximum of approximately 246 PK evaluable subjects at Week 32, denoted as N_{max}.

After (approximately) 86 subjects have had their Week 32 primary endpoints assessment and are PK evaluable the variability of $AUC_{\tau, 30\text{-}32}$ and $C_{max, 30\text{-}32}$ will be re-estimated based on the data of those $n_1 = 86$ subjects. This adequately allows the determination of the variability relevant for sample size re-calculation, which is in line with the primary endpoint analysis strategy. In order to mirror the primary endpoint analysis strategy the variability will be estimated after stage 1 as the residual variance from the model of ANCOVA as stated in Section 16.2.6 but, due to the blinded assessment, without the covariates 'Treatment' and 'Stage'.

The model will be:

Response ($AUC_{\tau, 30\text{-}32}$ or $C_{max, 30\text{-}32}$) = overall mean + logarithm* of rPASI + weight at Week 14 + ($AUC_{\tau, 12\text{-}14}$ or $C_{max, 12\text{-}14}$) + random error

*Natural logarithm

where:

rPASI is the ratio of PASI at Week 14 and PASI at Week 1 (continuous value). If PASI at Week 14 is zero, then the score from this Week 14 will be set to 0.05 (otherwise the logarithm is not defined)

This model will be implemented for both primary endpoints.

The maximum of the two estimated residual variances from the two models, $\hat{\sigma}_1^2$, together with the same assumption for the treatment difference as before (i.e. 8% on the ratio scale) will then be employed to calculate the updated total number $\widehat{N}$ required to achieve at least 80% power. To this end, the power/sample size calculation method by Fieller's theorem as described in [3, chapter 10.3.1] will be used.

This functionality is implemented in the function sampleN.RatioF from the R package PowerTOST (v. 1.4-3). That is, the following function call will be used to calculate $\widehat{N}$

sampleN.RatioF(alpha=0.049, CV=$\frac{\widehat{\sigma_1}}{m}$, theta0=0.92, targetpower=0.8, design="parallel"),

where m is the predicted mean response of a patient with average covariate values (LSMean) and theta0 represents the mean ratio assumed for sample size (re-)calculation.

In this study the final sample size shall not be lower than the initially planned size Nmin and therefore the resulting final total sample size $\widehat{\mathrm{N}}_\mathrm{f}$ is not smaller than the maximum of the two numbers Nmin and $\widehat{\mathrm{N}}$. In addition, a maximum sample size Nmax as described above will be used as cap, i.e. $\widehat{\mathrm{N}}_\mathrm{f} = \min(\max(\mathrm{N}_{\min}, \widehat{\mathrm{N}}), \mathrm{N}_{\max})$. The second stage, i.e. the study part after the blinded sample size reassessment of the study should thus include $\mathrm{n}_2 = \widehat{\mathrm{N}}_\mathrm{f} - \mathrm{n}_1$ PK evaluable patients.

BI has performed simulations to assess the actual type I error rate in the context of the planned blinded sample size re-estimation procedure in order to justify that the overall type I error is maintained.

The document of these simulations is presented in 0.

The ouputs of this analysis will provide:

- the two estimated residual variances from the two models (including corresponding CV)
- $\widehat{N}$
- n2
- CV for AUC_τ and C_{max} both at Week 14 and at Week 32. Note: here, it is considered as descriptive, i.e. no model applied here. Also include number of observations used.
- Number of subjects in PKS

16. PHARMACOKINETIC DATA

All PK analyses will be performed for the PKS.

Descriptive statistics of plasma concentrations and PK parameters will be also done on RTS. For PK parameter analysis on RTS the same rules regarding exclusion as for PKS will be applied.

16.1. GENERAL PHARMACOKINETIC CONSIDERATIONS

The PK parameters will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' [001-MCS-36-472] (see APPENDIX 4). Parameters, which are taken directly from the observed plasma concentration (e.g. C_{min}, C_{max}, C_{pre}, C_{50}, C_{58}) will be excluded from descriptive statistics and statistical analysis of PK endpoints if the corresponding plasma concentration is flagged to be excluded from descriptive statistics.

For technical reasons if PK blood sample at visit 9 or 18 is taken before 336 h after preceding dose and the plasma concentration of visit 9 or 18 is higher or equal than the preceding plasma concentration, then the time of the PK sample at visit 9 or 18 will be set to 336 h.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK parameters. Concentrations used in the PK calculations will be in the same format provided in the bioanalytical report (that is, to the same number of decimal places provided in the bioanalytical report).

If a measured level for a given PK sample is BLQ then 1/2 LLOQ of the assay (0.0125 µg/mL) will be used for the parameter calculations. For samples taken at baseline (visit 2) BLQ values will not be replaced by 1/2 LLOQ.

For data presentation the following conventions will apply:
All the sampling visits performed after an incorrect (not as randomized) administration of trial drug will be reported and flagged in the table. The flagged sampling results will be excluded from the descriptive statistics and from the figures. The planned and actual times are listed in a separate table in the CTR. In case a concentration value is excluded from the statistical and/or pharmacokinetic evaluation, it will be flagged appropriately in the respective concentration-time table.

The individual values as well as descriptive statistics are reported with 3 significant digits.

16.2. PHARMACOKINETIC ENDPOINTS

16.2.1. PRIMARY PHARMACOKINETIC VARIABLES AND DERIVATIONS

Pharmacokinetics will be assessed as the primary objective in this trial.

The primary pharmacokinetic endpoints are:

- $AUC_{\tau, 30\text{-}32}$ (Area under the adalimumab plasma concentration-time curve over the dosing interval of Week 30-32)
- $C_{max, 30\text{-}32}$ (Maximum observed adalimumab plasma concentration during the dosing interval Week 30-32)

16.2.2. SECONDARY PHARMACOKINETIC VARIABLES AND DERIVATIONS

The secondary pharmacokinetic endpoints are:

- $C_{min, 30-32}$ (Minimum observed adalimumab plasma concentration during the dosing interval Week 30-32)
- $t_{max, 30-32}$ (Time to maximum observed adalimumab plasma concentration during the dosing interval Week 30-32)

16.2.3. HANDLING OF MISSING DATA

Handling of missing PK data will be performed according to the relevant SOP of the sponsor.

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered (calculations and graphical representation). Descriptive statistics of concentrations at specific visits will be calculated only when at least 2/3 of the individuals have concentration measurements within the validated concentration range of the assay (that means between lower and upper limit of quantification as reported in the BA transfer) or BLQ values have been replaced by ½ LLOQ of the bioanalytical assay. The overall sample size to decide whether the "2/3 rule" is fulfilled will be based on the total number of samples actually drawn and not flagged as taken after an incorrect (not as randomized) administration of trial drug for that visit (i.e., BLQ (only if not replaced by ½ LLOQ of the bioanalytical assay), NOR, NOS, NOA and NOP are included).

If actual PK sampling date is missing the dosing date of the the same visit will be used instead.

If actual PK dosing date is missing the PK sampling date of the the same visit will be used instead.

If actual dosing time is missing and the dosing and PK sampling dates are identical then the PK sampling time of the the same visit will be used instead.

If actual PK sampling time for pre-dose PK samples is missing and the dosing and PK sampling dates are identical then the dosing time of the same visit will be used instead

If actual PK sampling time for sub-visits 8a-d or 17a-d is missing, the clock-time of preceding dosing will be used instead. Missing PK sampling dates of sub-visits 8a-d and 17a-d will not be replaced.

If it is not possible to impute missing date or times, the respective date or time will stay missing.

Imputed administration or PK sampling date and times will be listed in Appendix 14.2 of the CTR.

If weight is missing at Week 14 the last available measurement which is closest to week 14 used as Week 14 weight.

16.2.4. CHANGE OF PK PARAMETERS NAMES

Due to technical reasons parameter names in Appendix 14.2 will differ from the CTP and the remaining CTR sections (refer to table 16.2.2: 1).

Table 16.2.2: 1

	Appendix 14.2	Description
$C_{max,12-14}$	$C_{max,12}$	Maximum observed adalimumab plasma concentration during the dosing interval Week 12-14
$t_{max,12-14}$	$t_{max,12}$	Time to maximum observed adalimumab plasma concentration during the dosing interval Week 12-14
$C_{min,12-14}$	$C_{min,12}$	Minimum observed adalimumab plasma concentration during the dosing interval Week 12-14
$t_{min,12-14}$	$t_{min,12}$	Time to minimum observed adalimumab plasma concentration during the dosing interval Week 12-14
$AUC_{\tau,12-14}$	$AUC_{\tau,12}$	Area under the adalimumab plasma concentration-time curve over the dosing interval of Week 12-14
$C_{max,30-32}$	$C_{max,30}$	Maximum observed adalimumab plasma concentration during the dosing interval Week 30-32
$t_{max,30-32}$	$t_{max,30}$	Time to maximum observed adalimumab plasma concentration during the dosing interval Week 30-32

$C_{min,30-32}$	$C_{min,30}$	Minimum observed adalimumab plasma concentration during the dosing interval Week 30-32
$t_{min,30-32}$	$t_{min,30}$	Time to minimum observed adalimumab plasma concentration during the dosing interval Week 30-32
$AUC_{\tau,30-32}$	$AUC_{\tau,30}$	Area under the adalimumab plasma concentration-time curve over the dosing interval of Week 30-32

16.2.5. ANALYSIS OF PHARMACOKINETIC VARIABLES

Descriptive statistics of plasma concentrations and PK endpoints, as well as the tables and graphs for the pharmacokinetic noncompartmental analyses, will follow specific definitions of this SAP or, otherwise, the BI standard procedure "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" [001-MCS-36-472] (see APPENDIX 4).

16.2.6. ANALYSIS OF PRIMARY PHARMACOKINETIC ENDPOINTS

Pharmacokinetic parameters of a patient will be included in the statistical analyses of PK endpoints (ANCOVA) if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK.

The primary objective of this trial is to test the hypothesis of PK similarity between the switching arm and continuous Humira® arm) on the two PK parameters: $AUC_{\tau, 30-32}$ and $C_{max, 30-32}$.

The test for PK similarity will be performed with respect to the switching vs. continuous Humira® arm.

For the primary endpoint analysis the BE margins 80% – 125% on the ratio scale will be applied.

The hypotheses for the primary endpoint analysis can be written as follows:

- H01: Ratio of the means of $AUC_{\tau, 30-32}$ (switching arm versus continuous Humira® arm) is less than 80% or more than 125%
- H11: Ratio of the means of $AUC_{\tau, 30-32}$ (switching arm versus continuous Humira® arm) is within [80%, 125%]

and

- H02: Ratio of the means of $C_{max, 30-32}$ (switching arm versus continuous Humira® arm) is less than 80% or more than 125%
- H12: Ratio of the means of $C_{max, 30-32}$ (switching arm versus continuous Humira® arm) is within [80%, 125%]

A significance level of 4.9% was chosen to ensure overall type I error control at 5%, in light of the adapted analysis strategy. Details are provided in APPENDIX 5.

The two endpoints are considered coprimary (i.e., the trial is considered positive if the results for both endpoints are simultaneously positive), therefore no multiplicity-adjustment with respect to the alpha level will be performed.

The statistical model used for the analysis of $AUC_{\tau, 30-32}$ and $C_{max, 30-32}$ will be an analysis of covariance (ANCOVA) model. This model will include effects accounting for:

- Treatment (switching arm versus continuously Humira® arm)
- Logarithm* of rPASI, where rPASI is the ratio of PASI at Week 14 and PASI at Week 1 (continuous value). If PASI at Week 14 is zero, then the score from this Week 14 will be set to 0.05 (otherwise the logarithm* is not defined). Note that this imputation is only done for the purpose of creating the covariate used in this PK analysis.
- Weight at Week 14 (continuous value)
- Stage, where stage represents the two parts of the study prior to and after the blinded sample size reassessment (categorical, 1 or 2)
- $AUC_{\tau, 12-14}$ or $C_{max, 12-14}$ (continuous value)

* Natural logarithm

as a source of variation. As the measurements at Week 14 will be prior to randomization and all subjects will have received the same treatment with the reference treatment only, the covariates listed above are all considered adequate baseline values.

All effects will be considered as fixed. The model is described by the following equation:

(M1) response ($AUC_{\tau, 30-32}$ or $C_{max, 30-32}$) = overall mean + treatment effect + logarithm* of rPASI + weight at Week 14 + stage + ($AUC_{\tau, 12-14}$ or $C_{max, 12-14}$) + random error.

* Natural logarithm

where the random errors are assumed to be independent and normally distributed with zero mean and variance σ^2.

The analysis will then be adjusted for the covariates as stated in M1. The model will be implemented with the SAS® procedure PROC MIXED in conjunction with the LSMEANS statement. The LSMEANS statement is used to estimate the treatment LSMeans of the switching and non-switching arms which will be used to construct the point estimate for the ratio of means. The CI will be derived based on Fieller's theorem ([3], chapter 3.3.3.1 and 0):

All subjects that finished Week 32 Visit at or before the cut-off date will be allocated to stage 1. All other subjects (i.e., all subjects that at cut-off date do not have a finished Week 32 Visit) will be allocated to stage 2.

Equivalently ([3], chapter 10.2.1) to rejecting both null hypotheses for the primary endpoints, PK similarity between Switching arm and Continuous Humira® arm will be concluded if the two-sided 90.2% Fieller CI for the ratio of the means is fully contained within the standard equivalence limits of 80.00% to 125.00% and

$$\frac{|\bar{Y}_R|}{\hat{\sigma}\sqrt{\frac{1}{n_R}}} > t_{1-\alpha,df}$$

where $\bar{Y}_R$ refers to the LSMean of the reference treatment, $\hat{\sigma}$ is the residual standard deviation from the ANCOVA model (M1), df are the residual degrees of freedom of (M1) and $\alpha = 4.9\%$.

16.2.7. ANALYSIS OF SECONDARY VARIABLES

The secondary PK endpoint $C_{min,\ 30\text{-}32}$ will be analyzed in the same way as the primary endpoints However, only the mean ratio and CIs will be calculated and presented.

No formal comparison to margins will be performed.

The secondary PK endpoint $t_{max,\ 30\text{-}32}$ will be analyzed in a descriptive manner only.

17. EFFICACY OUTCOMES

17.1. SECONDARY EFFICACY ENDPOINTS

All efficacy analyses will be performed for the PPS.

17.1.1. MISSING DATA METHOD FOR SECONDARY EFFICACY ENDPOINTS

17.1.1.1. Missing Data Method: Non-Responder Imputation and Multiple Imputation

For the secondary efficacy analysis, missing PASI score at Week 32 and static Physician's Global Assessment (sPGA) at Week 32 data will be imputed using a combination of non-responder imputation (NRI) and multiple imputation (MI) methods. PASI and sPGA will be log-transformed using natural logarithm in the models.

As the same missing data method will be applied on the PASI score and the sPGA, these two endpoints will be named SCORE in this Section 17.1.1.

Unscheduled visits are in general not included in the analysis in this approach. However if a planned visit was missing and an unscheduled visit was performed within this visit window (refer to CTP section 6.1). The visit closest to the planned visit date will be used for the analysis.

The following table details exactly where the NRI / MI imputation method will be applied for the secondary efficacy analysis.

Table 1: Application of NRI / MI for the analysis on the PPS

	prior to/on Week 32	
Secondary efficacy analysis (PPS)	Discontinued treatment[#]	Did NOT discontinue treatment
SCORE computable using observed data at Week 32	NRI applied	Observed
SCORE NOT computable using observed data at Week 32	NRI applied	MI applied

[#] lost to follow-up (according to eCRF record for "End of Treatment" or "Trial Completion") is also included here, or subjects who took a therapy that may significantly impact efficacy assessment prior to this time-point.

The following steps will be followed:

17.1.1.2. Multiple Imputation

STEP 1:

- Creation of monotone missing data datasets:

A monotone missing data structure means the variables have a specific order and that missing data always occur at the end of data records. Once a variable measurement is missing, all subsequent variable measurements are missing.

A non-monotone missing data structure means the missingness of data doesn't depend on the order of the variables. Once a variable measurement is missing, the following variable measurements might be recorded or missing.

The first step of the multiple imputation is to transform a non-monotone missing data structure to a monotone one.

Intermediate missing variables will be multiple imputed using the Markov Chain Monte Carlo (MCMC) method and assuming Missing At Random (MAR) and multivariate Normality. The SAS procedure PROC MI with the MCMC option will be used.

The number of burn-in iterations before the first imputation and between each imputation has been identified based on approximately 90% of subject data up to Week 32 and fixed to 200.

This step will be performed on the longitudinal continuous PASI score and sPGA score (between Week 0 and Week 32).

Baseline value will be imputed only if both Screening and Day 1 values are missing. Otherwise, the last available value will be considered as baseline value.

One thousand imputations will be performed. A SAS dataset will be provided and will contain 1000 databases with a monotone missing data structure regarding the SCORE (PASI or sPGA) variables at each visit.

- Creation of non-missing data datasets:

The datasets, now with monotone missing data, will be imputed further using sequential regression, with the following model for each visit by treatment:

Log(SCORE) = + $Weight_{W14}$ + Stage + <log(Pasi Previous baseline score) + Log(Pasi Post-baseline score) >

That means, if the screening visit is Visit 1 and score (PASI or sPGA) at Visit v is denoted Sv, then for example the model to impute score S for Visit 4 will include observed S1 and S2; the model for Visit 5 will include observed S1, S2 and S4.

This model includes fixed effects of:

Treatment (switching arm versus continuously Humira® arm)

Weight at Week 14 (continuous value)

Stage, where stage represents the two parts of the study prior to and after the blinded sample size reassessment (categorical, 1 or 2)

The PASI75 and sPGA ≤ 1 at Week 32 will then be calculated for each of the multiple imputed datasets.The PASI and sPGA at Week 32 will be the only imputed values used in the next analyses. The missing PASI and sPGA values at previous visits and at baseline were imputed only in order to make the W32 imputation possible but will be used nowhere else.

17.1.1.3. Non Responder Imputation

STEP 2:

The imputed PASI75 and sPGA at Week 32 will be set to non-responder at Week 32 if the subject:

- discontinue treatment prior to Week 32 (including death)
- are lost-to-follow-up (according to eCRF record for "End of Treatment" or "Trial Completion") prior to Week 32
- have any severe violation related to any therapy that may significantly impact efficacy assessment prior to Week 32

Severe violation related to any therapy (according to CTP Table 4.2.2.1: 1) that may significantly impact efficacy assessment will be assessed by providing to the trial medical advisor:

- a list of medication codes (WHO Drug Dictionary version September 2016 or higher) presented in CTP Table 4.2.2.1: 1 and taken by at least one subject during trial conduct.
- full individual concomitant medication information including dose, frequency and Study day at start of medication.

Trial medical advisor will then identify the medications and start date of severe violation which may impact efficacy assessment.

17.1.2. Analysis of Secondary Efficacy Endpoints

The difference in proportions will be calculated between the two treatment arms as the difference between the observed proportions in each treatment group. Confidence intervals for the difference of proportions will be obtained using the Wald method, which is based on the asymptotically normal approximation to the distribution of the observed sample proportions.

The 90% and 95% CIs will be provided.

The difference in proportion will be calculated as: $p_1 - p_2$

This confidence interval formula is:

$$CI_{\alpha/2} = (p_1 - p_2) \pm z_{\alpha/2} \times \sqrt{\frac{p_1 \times (1 - p_1)}{n_1} + \frac{p_2 \times (1 - p_2)}{n_2}}$$

where:

p_1 = Observed proportion of subjects in the switching arm

p_2 = Observed proportion of subjects in the continuous Humira® arm

α = 10% for 90% CI bounds

5% for 95% CI bounds

$z_{\alpha/2}$ = 1.64 for 90% CI bounds

1.96 for 95% CI bounds

n_1 = Number of subjects in the switching arm

n_2 = Number of subjects in the continuous Humira® arm

17.1.2.1. Secondary Efficacy Variables and Derivations

The proportion of subjects with a PASI75 response will be assessed at Week 32.

- Relative change of PASI score (%) at Week 32 = (PASI score at baseline – PASI score at Week 32)/ PASI score at baseline x 100

In case of baseline value equal to 0 and non-missing value recorded at Week 32, then the change is set to 0% for the corresponding visit.

In this case, baseline is only the baseline value obtained before Reference Run-in Start Date. Baseline value obtained before Reference Double-blind Start Date is not used here.

- PASI75 at Week 32:
  - Yes if relative change of PASI score at Week 32 $\geq$ 75
  - No if relative change of PASI score at Week 32 < 75

The proportion of subjects with a static Physician's Global Assessment (sPGA) $\leq$ 1 (clear or almost clear) will be assessed at Week 32.

18. SAFETY OUTCOMES

For the Final analysis, safety analyses will be done on overall Trial period (W1-W58) and separately on Run-in Period (W1-W14) and Post-Randomization Period (W14-W58).

The overall Trial analysis, Double-Blind Period analysis and Post-Randomization Period analysis will be performed for the TS. The Run-in Period analysis will be performed for the RTS.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

Safety will be assessed as a secondary and further objective in this trial.

The safety endpoint is defined as the proportion of subjects with drug-related Adverse Events (AEs). This safety endpoint is considered a secondary endpoint in this trial.

Other safety endpoints are:

- Proportion of subjects with AEs, Serious AEs (SAEs), and AEs of Special interest (AESIs)
- Proportion of subjects with injection site reactions

18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 20.0 or higher. The system organ classes will be sorted by internationally agreed EMA SOC order (refer to APPENDIX 3); preferred terms will be sorted by decreasing frequencies (within system organ class).

A summary of the number of subjects and percentages within each of the categories described in the sub-section below will be provided.

In case of worsening in severity, a new entry is created with start date equal to start of worsening.

Listings will include Treatment-Emergent Adverse Events (TEAEs) and Non-TEAEs.

18.1.1. ADVERSE EVENT SPECIFIC DERIVATION

18.1.1.1. Treatment Emergent Adverse Event

According the period analysed, 3 derivations of the Treatment Emergent Adverse Events (TEAEs) will be used.

For the overall Trial analysis:

- TEAEs are defined as AEs that started or worsened on or after the first dose of Humira® and prior to the last dose of trial post-randomization medication + 10 weeks (W58).
- Non-TEAEs will be classified as “Screening” if AE start date is strictly prior the first dose of Humira® date. Non-TEAEs will be classified as “Post treatment” if AE start date is strictly after the last dose of trial post-randomization medication date + 10 weeks.

For the Post-Randomization Period analysis:

- TEAEs are defined as AEs that started or worsened on or after the first dose of trial post-randomization medication and prior to the last dose of trial post-randomization medication + 10 weeks (W58).
- Non-TEAEs will be classified as “Screening” if AE start date is strictly prior the first dose of trial post-randomization medication date. Non-TEAEs will be classified as “Post treatment” if AE start date is strictly after the last dose of trial post-randomization medication date + 10 weeks.

For the Run-in Period analysis

- TEAEs are defined as AEs that started or worsened on or after the first dose of Humira® and

prior to the first dose of trial post-randomization medication +10 weeks.

- Non-TEAEs will be classified as "Screening" if AE start date is strictly prior the first dose of Humira® date. Non-TEAEs will be classified as "Post treatment" if AE start date is strictly on or after the first dose of trial post-randomization medication date +10 weeks.

See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case, i.e., treatment-emergent in the period of the last injection of trial medication.

18.1.1.2. Risk ratio

Risk ratios and associated 95% exact confidence interval will be presented for adverse events of special interest.

18.1.2. ALL TEAEs

Number of subjects, percentages, and number of events will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum intensity and relationship to trial medication.

18.1.2.1. Intensity

Intensity is classed as mild/ moderate/ severe (increasing intensity). TEAEs starting after the first dose of Humira® or trial post-randomization medication (according to the analyzed period) with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst case intensity will be used in the corresponding severity summaries.

18.1.2.2. Relationship to Trial Medication

A related AE is defined as a TEAE with the item "Causal Relationship between the event and the trial drug" ticked "Related" on the AE form of the eCRF according to the investigator.

TEAEs with a missing relationship to trial medication will be regarded as related to trial medication. If a subject reports the same TEAE more than once for the given period within that SOC/ PT, the TEAE with the worst case relationship to trial medication within that period will be used in the corresponding relationship summaries.

All drug related AEs will be listed.

18.1.3. TEAEs Leading to Discontinuation of Trial Medication

TEAEs leading to permanent discontinuation of trial medication will be identified by using the "Action taken with trial drug due to AE" equal to "Drug Withdrawn" from AEs eCRF pages.

The number and percentages of subjects with TEAEs leading to permanent discontinuation of trial medication will be prepared by SOC and PT.

The AEs causing treatment modification or drug withdrawal will be listed.

18.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared including the number of subjects, percentages and number of events.

Non-Serious TEAEs with incidence in preferred terms strictly greater than 5% in at least one of treatment groups by SOC and PT will also be displayed.

A summary of related SAEs by SOC and PT will also be prepared.

The SAEs and Non-SAEs will be listed.

18.1.5. Adverse Events Leading to Death

TEAEs leading to Death are those events that are recorded as "Fatal" on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared overall including the number of subjects, percentages and number of events.

18.1.6. Other Safety Endpoints and Adverse Events Of Special Interest

A summary of the number of subjects, percentages, and number of events within each of the categories described in the sub-section below will be provided by SOC and PT.

The below table describes the allocation of adverse events to AESI group and other safety endpoints group:

Adverse Event :	AESI	Other safety endpoint
Serious infections	√	√
Hypersensitivity reactions	√	√
Drug induced liver injury	√	√
Injection site reactions		√
Anaphylactic reactions	√	√

18.1.6.1. Reported by Investigator

AESI reported by Investigators are those events recorded as “Adverse Event of Special Interest” equal to “Yes” on the Adverse Events page of the eCRF.

AESI reported by investigators and CTP specified are detailed in the following sections.

18.1.6.2. Serious Infections

Infections are those events with a SOC equal to “Infections and infestations".

Serious infections are:

- AEs which are both infections and SAEs as reported on the Adverse Events page of the eCRF.
- AEs which are both infections and identified by the medical advisor as requiring class IV (intravenous) antibiotics.
- Serious infection events of special interest (Serious infection AESI) are those events both identified as serious infection adverse events and recorded as “Adverse Event of Special Interest” equal to “Yes” on the Adverse Events page of the eCRF.
- Infections and Serious Infections will be summarized. Infections / Serious Infections will also be listed. The listing will include the “Adverse Event of Special Interest” equal to “Yes” information from the Adverse Events page of the eCRF as a flag.

18.1.6.3. Hypersensitivity Reactions

Hypersensitivity reactions are those events recorded as MedDRA code in the pre-defined Standardized MedDRA Queries (SMQ) “Hypersensitivity” (narrow).

Hypersensitivity reaction adverse events of special interest (Hypersensitivity reactions AESI) are those events both identified as Hypersensitivity reaction adverse events and recorded as “Adverse Event of Special Interest” equal to “Yes” on the Adverse Events page of the eCRF.

Hypersensitivity reactions will also be listed. The listing will include the “Adverse Event of Special Interest” equal to “Yes” information from the Adverse Events page of the eCRF as a flag.

18.1.6.4. Drug Induced Liver Injury (DILI)

Drug Induced Liver Injury (DILI) are those events identified by medical advisor on the subset of AEs for subjects presenting laboratory potential DILI findings (refer to Section 18.4.1).

DILI events of special interest (DILI AESI) are those events both identified as DILI adverse events and recorded as "Adverse Event of Special Interest" equal to "Yes" on the Adverse Events page of the eCRF.

Drug Induced Liver Injury (DILI) will be listed. The listing will include the "Adverse Event of Special Interest" equal to "Yes" information from the Adverse Events page of the eCRF as a flag.

18.1.6.5. Anaphylactic reactions

Anaphylactic reactions are those events recorded as MedDRA code in the pre-defined Standardized MedDRA Queries (SMQ) = "Anaphylactic reactions" (narrow)

Anaphylactic reaction adverse events of special interest (Anaphylactic reaction AESI) are those events both identified as Anaphylactic reactions and recorded as "Adverse Event of Special Interest" equal to "Yes" on the Adverse Events page of the eCRF.

Anaphylactic reactions will also be listed. The listing will include the "Adverse Event of Special Interest" equal to "Yes" information from the Adverse Events page of the eCRF as a flag.

18.1.7. AEs Occuring After the Last Injection For Subjects Discontinued Due to Lack of Efficacy

Subjects who discontinued treatment due to lack of efficacy will be identified from "End of treatment visit" eCRF page, where "Reason for End of Treatment" is "Lack of Efficacy".

Number of subjects, percentages, and number of events occurring after the last injection and prior to the last injection + 10 weeks for subjects discontinued due to lack of efficacy by SOC and PT will be prepared.

AEs occurring after the last injection and prior to the last injection + 10 weeks for subjects discontinued due to lack of efficacy will be listed.

18.2. INJECTION-SITE REACTIONS

Injection-site reactions are those events recorded with MedDRA high level terms (as listed in BIcMQs Administration site reaction subsearches 1, 2, 4 and 5, with a version consistent with the MedDRA version, refer to APPENDIX 4):

- Administration site reactions NEC
- Application and instillation site reactions
- Infusion site reactions
- Injection site reactions
- Moreover, the number and percentage of subjects with injection site reactions will be summarized for

each injection site reaction (Swelling / Hardening / Heat / Redness / Pain / Itching / Bruising / Other).

- Injection-site reactions will be listed.

18.3. DEATHS

If any subjects die during the trial as recorded on the "End of Treatment" page or the "Trial Completion" page or the "Safety Follow-Up" page or the AE page (SAE which "Results in death" or AE with "Fatal" outcome) or the "Death" form, the information will be presented in a summary table and a data listing.

18.4. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this trial for Serum Chemistry, Hematology and Urinalysis. A list of laboratory assessments to be included in the outputs is included in APPENDIX 7.

Presentations will use SI and US Units.

Quantitative laboratory measurements reported as "< X", i.e., below the lower limit of quantification (BLQ), or "> X", i.e., above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the listings.

Qualitative laboratory urinalysis results measured by central laboratory will be classified to the categories "Positive" and "Negative" based on the central laboratory normal reference.

The handling of retests, unscheduled, and end of trial measurements is described in Section 6.3. However, laboratory values taken after the first dose of analyzed period up to the end of the period (periods described in Section 18) will be assigned to the treatment phase for evaluation. Moreover, tables about DILI and hemoglobin will include unscheduled visits.

All available data will be listed.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Shifts from baseline category (Low/ Normal/ High) by visit (except for urinalysis)
- Shift from baseline category (Negative/ Positive) by visit (for urinalysis)
- Listing of subjects meeting abnormal criteria
- Proportion of possible Hy's law subjects
- Proportion of possible Drug Induced Liver Injuries (DILIs)
- The time course of ALT, AST and total bilirubin (TBL) for all possible Hy's law subjects, all parameters shown on a logarithm to base 10 scale of the multiple of the upper limit of normal (ULN) (Y axis) versus days since treatment start (X axis).

Scatter plots for Evaluation of Potentially Drug-Induced Liver Injury:

- Log ALT on the X axis and log TBL on the Y axis, both shown on a logarithm to base 10 scale of the multiple of the ULN
- Log AST on the X axis and log TBL on the Y axis, both shown on a logarithm to base 10 scale of the multiple of the ULN.

Baseline is described in Section 6.2.

18.4.1. LABORATORY SPECIFIC DERIVATIONS

Log ALT = logarithm to base 10 scale of the multiple of the ULN of ALT

Log AST = logarithm to base 10 scale of the multiple of the ULN of AST

Log TBL = logarithm to base 10 scale of the multiple of the ULN of TBL.

Note: Bilirubin value instead of TBL will be used.

- Potential Hy's law categories:
  - Category 1: ALT or AST >=3xULN and TBL >=2xULN within the same sample
  - Category 2: TBL >=2xULN within 30 days after transaminase peak (ALT or AST >=3 ULN)
- Potential Hy's Law subjects are defined as subjects with laboratory data in at least one Potential Hy's law categories at any time point of the trial.
- Drug induced liver injury (DILI):
  - Normal liver function at Baseline is defined as AST and ALT and Total Bilirubin values measured at baseline are each <= respective ULN.
  - For post baseline visits:
    - Subjects with normal liver function at Baseline and (AST and/or ALT ≥3 times ULN and TBL ≥2 times ULN within the same sample).
    - Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

18.4.2. LABORATORY REFERENCE RANGES AND ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

Low: Strictly below the lower limit of the laboratory reference range.

Normal: Within the laboratory reference range (upper and lower limit included).

High: Strictly above the upper limit of the laboratory reference range.

18.4.3. OTHER SAFETY LABORATORY EVALUATIONS

18.4.3.1. Pregnancy test

Descriptive table will present pregnancy results for females by visit on TS.

The pregnancy results will be listed as well.

18.4.3.2. Tuberculosis test

Descriptive table will present Tuberculosis (TB) test results by visit on TS.

The TB test results will be listed as well.

18.5. ECG EVALUATIONS

Results from ECGs will be summarized by visit to the categories as recorded in the eCRF page "12-Lead-ECG" ("Normal", "Abnormal, not clinically significant" and "Abnormal, clinically significant").

ECG evaluations will also be listed.

18.6. VITAL SIGNS

The following Vital Signs measurements will be reported:

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Pulse Rate (bpm)
- Temperature (^{0}C)
- Weight will be presented along with vital signs.
- Weight (kg)

The handling of retests, unscheduled, and end of trial measurements is described in Section 6.3.

The summary of actual and change from baseline by visit will be provided for vital sign data. In case of multiple measurement timepoints at one visit, the pre-injection data will be used for summary tables.

Vital signs data will be listed.

18.7. PHYSICAL EXAMINATION

Incidence of evaluation categories (Normal, Abnormal) at baseline and post-baseline visits will be provided for

physical examination data.

The handling of retests, unscheduled, and end of trial measurements is described in Section 6.3.

Baseline is described in Section 6.2.

19. IMMUNOGENICITY

19.1. MISSING DATA METHODS FOR IMMUNOGENICITY

Missing data will not be imputed.

19.2. ANALYSIS OF IMMUNOGENICITY VARIABLES

Immunogenicity will be assessed as secondary and further objectives in this trial. All Immunogenicity analyses will be performed based on (i) RTS without patients being randomized (if feasible) and (ii) TS.

There will be no formal statistical comparisons between the treatment groups for Immunogenicity data.

The handling of retests, unscheduled and end of trial measurements are described in Section 6.3.

The following analyses will be performed:Number and frequency of subjects with ADA / neutralizing ADA sampling results by actual treatment arm and visit*:

- Negative
- Positive
- Total reportable (= sum of Negative and Positive)
- Not Reportable (= samples which should have been taken per protocol but no result is available (due to many reasons). Samples from subject that discontinued (drop-outs) or subjects that have not reached a defined time-point yet, are not considered non-reportable but reduce the number of total samples available)
- Total (= sum of Total Reportable and Not Reportable)

Descriptive statistics of ADA and nAb titer will be provided by actual treatment arm and visit when available.

* where ADA/nAb samples have been taken, i.e. Visits 2, 3, 6, 8, 9, 11, 13, 17, 18, 22, 27 and 28. Note that patients from the RTS that have not been randomized, by definition, do not have all values available for Visit 11 onwards, see CTP.

The ADA and nAbs results will be listed as well.

ADA and nAbs results listing restricted to the subjects treated at least once with the incorrect trial treatment will

be provided.

From those assessments, the secondary immunogenicity endpoints are:

- The proportion of subjects with ADAs at Week 32 (Visit 18).
- ADA titer of subjects with ADAs at Week 32 (Visit 18).
- The proportion of subjects with neutralizing Antibody (nAb) at Week 32 (Visit 18)
- nAb titer of subjects with nAbs at Week 32 (Visit 18).

All other time points are considered further immunogenicity endpoints.

The following figures will be provided for Immunogenicity data (only for TS):

- Time course (Bar Chart) of ADA development (percent positive subjects) over time (by planned study day) for all treatments.
- Box plot (with whiskers) of titer within ADA positive subjects over time (by planned study day) (one graph) – the log2 scale will be used
- Box plot (with whiskers) of titer within ADA positive subjects at each ADA timepoint (multiple graphs) – the log2 scale will be used
- Time course (Bar Chart) of nAb development (percent positive subjects) over time (by planned visit day) for all treatments
- Box plot (with whiskers) of titer within nAb positive subjects over time (by planned study day) (one graph) – the log2 scale will be used
- Box plot (with whiskers) of titer within nAb positive subjects at each ADA timepoint (multiple graphs) – the log2 scale will be used

20. REFERENCES

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