STATISTICAL ANALYSIS PLAN

1297.12

EFFICACY, SAFETY, AND IMMUNOGENICITY 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

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Please refer to Output Templates V2.0 (Dated 31JAN2018) for Protocol 1297.12.

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, immunogenicity, and pharmacokinetics data for Protocol 1297.12. 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 1.0, dated 26th of April 2016.

2. TRIAL OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this trial is to establish equivalence in efficacy between BI 695501 and US-licensed Humira at Week 16 in patients with active moderate to severe chronic plaque psoriasis.

2.2. SECONDARY OBJECTIVES

The secondary objectives of this trial are to compare the safety and efficacy profiles of BI 695501 and US-licensed Humira. Secondary efficacy endpoints are detailed in section 15.2 and safety endpoints are described in section 16.

3. TRIAL DESIGN

3.1. GENERAL DESCRIPTION

This is a multinational, randomized, double-blind, parallel-arm, multiple-dose, active comparator trial of BI 695501 and US-licensed Humira.

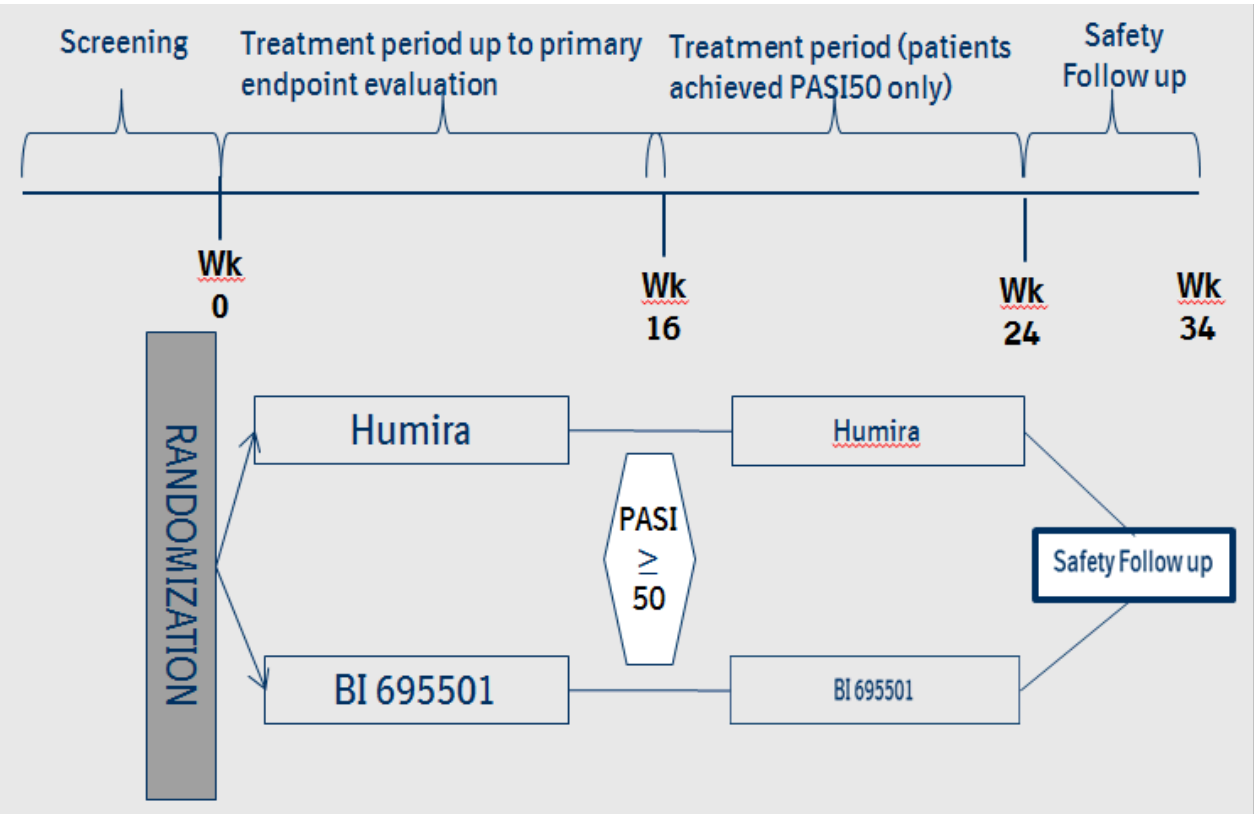
In total, approximately 300 patients with moderate to severe chronic plaque psoriasis are planned to be randomized in this trial.

Patients are included in the trial once they have signed the informed consent. Patients suitable after screening will be eligible to participate in the 24-week treatment period and will be randomized at a ratio of 1:1 in a blinded fashion to 1 of 2 treatment arms (BI 695501 or US-licensed Humira).

After Week 16, only patients who achieve at least a 50% reduction in Psoriasis Area and Severity Index (PASI 50) response will continue the trial receiving their randomized treatment up to Week 24. Those patients not achieving at least PASI 50 (or who discontinue the trial early), will not be treated with the trial drugs, but only followed up for safety.

All patients who receive at least 1 injection of BI 695501 will have a Safety Follow-up visit 10 weeks after the last dose of trial medication.

Diagram of 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

- Full Analysis Set (FAS) definition was updated in this SAP to include subjects with one component variable post-baseline (and not systematically the full score available)
- The randomization strata was not considered as a covariate in the primary endpoint analysis in the protocol. This has been updated in section 7.1 of this SAP. The reason for this change is that randomization strata should be included in the model to follow the ICH E9 guidelines. The same was done for the secondary efficacy endpoint analysis.
- The item score of DLQI was defined as ranging "from 0 (not relevant) and 1 (not at all) to 3 (very much)". This has been updated in section 10.1 of this SAP as "Every item score ranges from 0 (Not relevant/Not at all) to 3 (Very much)" to be consistent with DLQI scoring.
-
- The definition of drug induced liver injury was not correctly stated in the protocol. This has been updated in section 16.3.1 of this SAP.
- The primary endpoint has been rephrased as: "The proportion of subjects with *at least* 75% reduction in Psoriasis Area and Severity Index (PASI 75) response at Week 16" instead of "The proportion of subjects with *a* 75% reduction in Psoriasis Area and Severity Index (PASI 75) response at Week 16"
-

4. PLANNED ANALYSES

The following analyses will be performed for this trial:

- Primary Analysis (after primary endpoint is available)
- Final Analysis (after Database lock, based on all available data)

This document will provide details for Primary Analysis and Final Analysis.

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

4.1. PRIMARY ANALYSIS

The primary analysis will take place when the primary endpoint is available, i.e., after the last patient has completed the Week 16 visit. The corresponding calendar date will be referred to as the cut-off date (please refer to APPENDIX 4).

At the time of primary analysis, all available data up to and including the cut-off date will be considered. The Week 16 visit date of the last patient will be used as cut-off date for this analysis (please refer to APPENDIX 4). Only cumulated results will be presented, i.e., patient level data will be excluded meaning that N, mean and SD will be displayed instead of usual summary statistics. Indeed, there may be a risk for unblinding when presenting individual data such as minimum or maximum values, quartiles together with the treatment groups.

The study team, including those responsible for creating the programs to produce the outputs for the Primary Analysis, will remain blinded. Once the programs have been produced by the study team, these programs will be sent to an independent statistician from who will apply the randomization schedule and remove those tables that contain unblinding information due to sparse data (remove from delivery those tables where for any treatment groups only one subject is displayed). After this step, the independent statistician will provide Boehringer-Ingelheim with a set of outputs without patient level information.

4.2. FINAL ANALYSIS

A final analysis (including all endpoints) will be performed when all trial data are available, i.e., approx. 33 weeks after the last patient has been randomized. In this analysis, all analyses performed for the primary analysis will be repeated with the (partially) updated data, in particular with respect to safety data collected at Week 33 and efficacy endpoints collected at Week 33. The results of the final analysis will be summarized in a CTR.

5. ANALYSIS SETS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to the unblinding for primary analysis (Week 16).

5.1. ALL SUBJECTS ENROLLED SET [ENR]

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

5.2. 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.

5.3. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will contain all randomized patients who received at least 1 dose of trial medication, and have all efficacy measures relevant for the PASI 75, measured at baseline and at least once post-baseline (prior to or on Week 16). Post-baseline, at least one component variable should be available (not systematically the whole PASI score).

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

5.4. PER PROTOCOL ANALYSIS SET [PPS]

The per-protocol analysis set (PPS) will contain all subjects in the FAS 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. The important protocol violations relevant for efficacy until week 16 inclusive may include but are not limited to:

- Incorrect trial medication taken. Kit numbers which were actually used for the preparation of the trial drug will be recorded on the eCRF. If, on the patient level, at least one kit number used before Week 16 does not correspond to the initial randomized treatment group then this will be an important protocol violation.

- Severe violation of treatment compliance prior to Week 16: medical team will review subjects with treatment compliance outside 80% and 120% (refer to section 14.1) and decide if the violation is severe.

- Severe violation of inclusion/exclusion criteria

    - Exclusion criterion 2: Previous treatment with more than 1 biological agent, or adalimumab or adalimumab biosimilar. No prior biologic exposure within last 6 months of screening will be permitted

    - Exclusion criterion 6: Patients 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 study, or less than 30 days since ending another investigational device or drug study(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.

Subjects to be excluded from the PPS will be identified prior to the Data Snapshot/Database Lock. For criteria not assessable before unbinding (such as incorrect trial medication taken), the subjects will be identified after the Data Snapshot/Database Lock.

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

5.5. SAFETY ANALYSIS SET [SAF]

The safety analysis set (SAF) will contain all subjects in the RND set who receive at least one dose of trial medication.

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

For analyses and displays based on SAF:

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.

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. It will appear in every listing where an assessment date or event date appears.

Reference start date is defined as the day of the first dose of trial medication, (Day 1 is the day of the first dose of trial medication), or for subjects randomized but not treated it is the day of randomization.

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

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

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

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

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments) except for the primary efficacy endpoint (refer to section 15.1.2.2). In the case where the last non-missing measurement and the first dose of trial medication 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 5, 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 DILIs (refer to section 16.3).

Subjects who are terminated from the study early will have their End of Treatment (EoT) visit on a date which may or may not coincide with the window designated for one of the 8 regular planned visits.

Remapping of EOT visit assessment data to a regular scheduled visit will be performed only if the EOT visit

assessment was performed during the window for a regular scheduled visit and if the assessment value is non-missing for each regular planned visit between the last regular planned visit for which it was non-missing and the date of the EOT visit. Otherwise, the data will be classified as Early Termination and identified as such in the relevant listings.

If a subject's EOT visit for an assessment was performed in the window designated for a regular planned visit X and the last time point prior to visit X at which the assessment was to have been performed, according to the study flow chart, is the last regular planned visit for which it was non-missing then the assessment's value will be mapped to visit X, if it is an assessment that is scheduled to be performed at visit X.

If a subject's EOT visit for an assessment was performed at some time point after the window designated for a regular planned visit X and before the window designated for a regular planned visit X + 1 and the last time point prior to visit X + 1 at which the assessment was to have been performed, according to the study flow chart is the last regular planned visit for which it was non-missing then the assessment's value will be mapped to visit X + 1, if it is an assessment that is scheduled to be performed at visit X + 1.

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

The default significance level will be (5%); confidence intervals will be 95% and 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

6.7. SOFTWARE VERSION

All analyses will be conducted using 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 the primary and secondary efficacy analyses. For details of their inclusion in the models, see the specific analysis section.

- Treatment (BI 695501 or US-sourced Humira)
- Baseline PASI
- Prior exposure to a biologic agent (Yes / No).

7.2. MULTICENTER TRIAL

This trial will be conducted by multiple investigators at multiple centers internationally, approximately 50 clinical sites across approximately 10 countries. Randomization to treatment arms is stratified by prior exposure to biological agent. No stratification by site was planned because of the small number of subjects to be randomized per site.

7.3. MISSING DATA

Missing safety data will not be imputed, unless otherwise specified in section 16.

Missing efficacy data will be handled as described in section 15.

Calculation for a partial date is described in APPENDIX 2.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No multiplicity consideration is required in this trial.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be performed if the smallest group includes at least 10% of the randomized subjects.

7.5.1. REGION

A further subgroup analysis will be performed to evaluate the impact of the region on the primary efficacy endpoint. For this purpose, region will be defined as:

USA

Non-USA (Other countries)

7.5.2. PRIOR USE OF BIOLOGICAL AGENT

A further subgroup analysis will be performed to evaluate the impact of the stratification factor on the primary efficacy endpoint. For this purpose, the following stratification factor will be considered: prior use of biological agent Yes/No.

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.

9. DISPOSITION AND WITHDRAWALS

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)
- Full Analysis set (FAS)
- Per Protocol Analysis Set (PPS)
- Safety Analysis Set (SAF)
-

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.
- Randomized
- Randomized but not treated
- Treated
- Subjects with PASI 50 at Day 113 (Week 16)
- Subjects treated after Day 113 (Week 16)
- Completed treatment at Day 169 (Week 24)
- Completed the trial
- Discontinued from treatment strictly before Day 113 (Week 16), primary reason for premature discontinuation from treatment before Day 113 (Week 16)
- Discontinued from treatment, primary reason for premature discontinuation from treatment
- 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.
- Randomized

- Randomized but not treated
- Treated
- Subjects with PASI 50 at Day 113 (Week 16)
- Subjects treated after Day 113 (Week 16)
- Completed treatment at Day 169 (Week 24)
- Completed the trial

9.1. IMPORTANT PROTOCOL DEVIATIONS

Protocol violations (as defined in section 5.4), as well as inclusion and exclusion criteria violators will be tabulated and listed for the FAS.

Separately, important protocol violations (not systematically excluding from PPS) are defined as:

- entering the study even though the subject did not satisfy the entry criteria;
- developing withdrawal criteria during the study but the subject did not withdraw;
- receiving the wrong treatment or incorrect dose;
- receiving a prohibited concomitant treatment.

Important protocol violations confirmed by a clinical and medical review as recorded in the protocol deviations log will be tabulated and listed for the FAS. These violations are not necessarily excluding subjects from the PPS (for exclusions from PPS refer to section 5.4).

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 will be reported at Primary Analysis for the FAS, PPS, SAF, and at Final Analysis for RND, FAS, PPS, and SAF:

- Age (years) at Informed Consent
- Category of age groups at Informed Consent

- Adolescent (12-17 years): 12 <= AGE < 18 – no patient expected
- Adults (18-64 years): 18<= AGE < 65
- Adults (65-84 years): 65<= AGE < 85
- Adults (Over 85 years): 85<= AGE – no patient expected

- First age category at Informed Consent
  - AGE < 65 years
  - AGE >= 65 years
- Second age category at Informed Consent
  - AGE < 65 years
  - 65 <= AGE < 76
  - 76 <= AGE <85
  - AGE >= 85
- Gender (Male/Female)
- Childbearing potential (Post-Menopausal / Surgically Sterile / Childbearing Potential (includes tubal ligation))
- Race (American Indian or Alaska Native / Asian / Black or African American / Native Hawaiian or Other Pacific Islander / White / Other)
- Ethnicity (Hispanic or Latino / Not Hispanic or Latino / Not reported/ Unknown)
- Country
- Weight at baseline (kg)
- Height at baseline (cm)
- BMI at baseline (kg/m^2)

The randomization stratification categories (Prior exposure to a biological agent Yes/No) based on eCRF data, will be presented at Primary and Final Analyses for the FAS.

The following baseline disease characteristics will be presented at Primary Analysis for the FAS, SAF, and at Final Analysis for FAS, PPS, and SAF:

- PASI score at baseline as collected in the eCRF
- Static Physician's Global Assessment of psoriasis (sPGA) score at baseline

- Dermatology Life Quality Index (DLQI) score at baseline
-

Other baseline characteristics will be presented on FAS, and SAF:

- Infection screen (for HBsAg, HCV and HIV test)
- Chest X-Ray result
- Tuberculosis (TB) test
-

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

10.1. DERIVATIONS

- Conversion factors:
  - 1 lbs=0.453592 kg
  - 1 in=2.54 cm
- BMI (kg/ m^2) = weight (kg)/ height (m^2)
- DLQI

The questionnaire will be analysed under 6 headings as follows:

Domain	Question Number	Score
Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and school	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6

Treatment	Question 10	Score maximum 3

Every item score ranges from 0 (Not relevant/Not at all) to 3 (Very much). The domain score is obtained by summing the score of the corresponding items.

DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0-1 = no effect on subject's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on subject' s life. The higher the score, the more the quality of life is impaired. If the answer to 1 question in a domain is missing, that domain is treated as missing and the score calculated by summing the score of the 5 non-missing domains. If 2 or more questions are left unanswered (missing), DLQI total score is treated as missing.

-

11. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History information will be presented at Primary Analysis for the SAF, at Final Analysis fo the FAS, PPS and SAF.

Surgical and Medical History will be coded using MedDRA version 19.1 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.

- Prior medical history, surgeries, and procedures are defined as those conditions or procedures which stop prior to or at Screening.
- Concomitant medical history, surgeries, and procedures are defined as those conditions or procedure which:
  - started prior to or at Screening and are ongoing or active at the date of Screening
    or
  - started after Screening during the treatment period.

For rescreened patient 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

Medications will be presented at Primary and Final Analyses for the FAS, PPS, and SAF. 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.

- 'Prior' medications are medications which started and stopped prior to the first dose of trial medication.

- 'Concomitant' medications are medications which:

- started prior to, on, or after the first dose of trial medication and started no later than end of trial medication,
- AND ended on or after the date of first dose of trial medication or were ongoing at the end of the trial.

- 'Post' medications are medications which started after the last dose of trial medication.

In addition, concomitant medications will be allocated to Period 1 as follows:

- Period 1: Concomitant medication with start date prior to Week 16 visit date, and [end date after randomization or ongoing at the end of the trial].

13. TRIAL MEDICATION EXPOSURE

Exposure to trial medication will be presented at Primary Analysis for the SAF, at Final Analysis for the FAS, PPS and SAF.

The proportion of subjects treated at each planned visit (administration on Day 1, Day 8, and every other week until Day 162) and per treatment group will be presented.

Descriptive statistics for the number of injections from Day 1 up to Week 16 (included), from Week 16 (excluded) up to Week 24 and overall per subjects will be presented.

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

Exposure categories will be the following cumulative categories: >= 1 day, >= 2 weeks, >= 4 weeks, >=12 weeks, >=16 weeks, and >=24 weeks.

13.1. DERIVATIONS

The date of first and last trial medication administration will be taken from the eCRF page "Trial Medication Injection".

Duration of exposure (days) = (date of last injection - date of first injection + 1).

Duration of exposure (weeks) = Duration of exposure (days) / 7.

Patient Year Exposure (year) = cumulative duration of exposure in days per subjects / 365.25.

14. TRIAL MEDICATION COMPLIANCE

Compliance to trial medication will be presented at Primary Analysis for the SAF, at Final Analysis for the FAS, PPS and SAF.

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 follows and will correspond to the observed compliance between visit N and N-1:

Compliance (%) = (Number of administered injections at visit X)*100/Planned number of injections at visit X

Planned usage is detailed below.

- "Overall" compliance will be calculated as follows:

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

Where

Planned usage

Visit N	1	2	3	4	5	6	7	8	9

Number of injections between visit N and N-1	-	2	1	1	2	2	2	2	2
Planned cumulative number of injections	0	2	3	4	6	8	10	12	14

- "Week 16" compliance will be calculated considering the injections until Week 16 (visit 7) (included).

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy endpoint is:

- The proportion of subjects with at least 75% reduction in Psoriasis Area and Severity Index (PASI 75) response at Week 16

PASI reduction at Week 16 is assessed as the decrease relative to baseline measurement and expressed as a percentage:

- Reduction (%) = [100*(PASI at Baseline - PASI at Week 16)/PASI at Baseline]

In case of baseline value equal to 0 and non-missing post-baseline value recorded, then the change is set to 0% for the corresponding visit (no reduction).

Subjects with a reduction greater or equal to 75% are responders. Other subjects are considered as non-responders.

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

15.1.2.1. Missing Data Methods for Primary Analysis: Non-Responder Imputation and Multiple Imputation

For the primary analysis, missing PASI 75 data will be imputed using a combination of non-responder imputation (NRI) and multiple imputation (MI) methods.

Unscheduled visits are in general not included in the analysis in this approach. However if an unscheduled visit was performed within a visit window. 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 primary analysis.

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

	prior to/on Week 16	
Primary analysis (FAS)	Discontinued treatment[#]	Did NOT discontinue treatment
PASI 75 computable using observed data at Week 16	NRI	Observed
PASI 75 NOT computable using observed data at Week 16	NRI applied	MI applied

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

The following steps will be followed:

15.1.2.2. Multiple Imputation

STEP 1:

1. Creation of monotone missing data structure:

Intermediate (non-monotone) missing data will be multiple imputed using the Markov Chain Monte Carlo (MCMC) method and assuming MAR and multivariate Normality. The SAS procedure PROC MI with the MCMC option will be used.

The number of burn-in iterations has been identified based on approximately 90% of subject data up to Week 16 and fixed to 200.

This step will be performed on the longitudinal continuous PASI score (between Week 0 and Week 16), and SAS output for missing data pattern will be provided.

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.

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

PASI = Treatment + Prior exposure to a biological agent + <Previous baseline and Post-baseline data for the score>.

That is, if the screening visit is Visit 1 and PASI score S at Visit v is denoted S_v, then for example the model to impute PASI score S for Visit 4 will include observed S_1 and S_2; the model for Visit 5 will include observed S_1, S_2 and S_4.

This model includes fixed, categorical effects of:

- Treatment (BI 695501 versus US-sourced Humira)
- Prior exposure to a biologic agent (Yes versus No)

Note for 1 and 2: The seed 1000 will be used throughout. If a second seed is required, 1001 will be used, and so on as necessary.

The PASI 75 will then be calculated for each of the multiple imputed data sets.

15.1.2.3. Non Responder Imputation

STEP 2:

The imputed PASI 75 will be set to non-responder at Week 16 if the subject:

- discontinue treatment prior to Week 16

  or

- is lost-to-follow-up (according to eCRF record for "End of Treatment" or "Trial Completion") prior to Week 16

  or

- has any severe violation related to any therapy that may significantly impact efficacy assessment prior to Week 16

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

15.1.2.4. Missing Data Methods for Sensitivity Analysis: Non Responder Imputation and Last Observed Carried Forward

For the sensitivity analysis, missing PASI 75 data will be imputed using a combination of non-responder imputation and Last Observed Carried Forward (LOCF).

Only the data up to Week 16, inclusive, will be considered.

The following table details exactly where the NRI / LOCF imputation method will be applied for the sensitivity analysis.

Table 1: Application of LOCF / NRI for the primary analysis on the FAS

	prior to/on Week 16	
Primary analysis (FAS)	Discontinued treatment[#]	Did NOT discontinue treatment
PASI 75 computable using observed data at Week 16	NRI	Observed
PASI 75 NOT computable using observed data at Week 16	NRI applied	LOCF applied

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

The following steps will be followed:

a. Last Observed Carried Forward

STEP 1:
Missing PASI score will be imputed using LOCF method and PASI 75 will be calculated based on the imputed scores. Last observation will be carried forward as many times as needed.

b. Non Responder Imputation

STEP 2:
The imputed PASI 75 will be set to non-responder at Week 16 if the subject:

- discontinues treatment prior to Week 16
- are lost-to-follow-up (according to eCRF record for "End of Treatment" or "Trial Completion") prior to Week 16
- have any severe violation related to any therapy that may significantly impact efficacy assessment prior to Week 16

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

15.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary efficacy analysis will be performed for the FAS.

The primary objective of this trial is to test the hypothesis that BI 695501 and US-sourced Humira are equivalent.

The test for equivalence will be performed with respect to BI 695501 versus US-sourced Humira.

The hypotheses for the equivalence test can be written as follows:

- H_0: Difference in PASI 75 response rates at Week 16 (BI 695501 minus US-sourced Humira) is less than -18.0% or more than 18.0%

- H_1: Difference in PASI 75 response rates at Week 16 (BI 695501 minus US-sourced Humira) is within [-18.0%, 18.0%]

To conclude equivalence, the two-sided 95% CI of the difference in PASI 75 response rate (BI 695501 – Humira) rounded to 1 decimal place has to be fully within the equivalence limits of ± 18.0%.

The primary analysis of the difference in PASI 75 response rates at Week 16 will be based on logistic regression with subsequent transformation of the estimated parameters to the difference in proportions.

The estimates from the logistic regression are on the logit scale, and the difference in proportions will be calculated as the difference between the predicted probabilities in the treatment groups on the original scale, with the variance calculated using the cumulative distribution function method of Reeve (Reeve 2016).

The statistical model can be described as follows:

(M1) Logit (response to treatment at Week 16) = Treatment + Baseline PASI + Prior exposure to a biologic agent + random error

This model includes fixed, categorical effects of:

- Treatment (BI 695501 versus US-sourced Humira)

- Prior exposure to a biologic agent (Yes versus No)

and continuous effect of:

- Baseline PASI

The random error is assumed to be binomially distributed.

The analysis will consist of the following four steps:

STEP 1: Starting from the incomplete dataset, data imputation method are applied (described in section 15.1.2) to generate 1000 completed datasets.

STEP 2: Calculation of difference in proportion based on adjusted PASI 75 responders

The adjusted proportions of subjects with PASI 75 response in each groups at Week 16 are estimated from the logistics regressions on the logit scale, on each of the 1000 completed datasets.

The difference in proportions is calculated as the difference between the probabilities predicted by the model for both treatment groups on the original scale at Week 16.

STEP 3: Calculation of confidence intervals based on cumulative distribution function method of Reeve

The risk-difference confidence intervals are calculated on each completed datasets using the risk differences calculated in STEP 2) and the cumulative distribution function method of Reeve (Reeve 2016) with 1,000,000 simulations.

STEP 4: Computation of the final confidence interval

The estimated risk differences from STEP 2, and estimated standard errors back calculated using STEP 3 confidence intervals are combined using Rubin's Rules into the final confidence interval.

15.1.3.1. Calculation of difference in proportion (STEP 2 details)

The Week 16 endpoint will be analyzed using (M1) model.

The following SAS code will be used:

```
proc genmod data=data_PASI75_week_16 descend;
      class PASI75(ref="N") TRTP(ref="HUMIRA") EXPOS_BIO(ref="N") /
      param=GLM;
      model PASI75=TRTP BASELINE_PASI EXPOS_BIO/ dist=binomial  link=logit;
   lsmeans TRT / ilink OBSMARGINS diff=all;
run;
```

The population adjusted natural scaled proportion at Week 16 are the estimates produced by the LSMEANS statement.

15.1.3.2. Calculation of confidence interval (STEP 3 details)

The difference in proportion at Week 16 is produced in STEP 1.

The Week 16 confidence interval for the estimated difference in proportion are produced using the cumulative distribution function method of Reeve (Reeve 2016).

The SAS code to implement the method is provided in APPENDIX 6 and required as input:

1. Variance (g) is directly provided by SAS PROC GENMOD Empirical Standard Error Estimates.

2. $Cov(b_i, b_j)$ and $Cov(\gamma, b_i)$ $\forall i,j \in [0;k]$ are directly provided by SAS PROC GENMOD Covariance Matrix (Empirical).

3. Variance (z) will be calculated using the formula:

$$Var(z) = Var\left(b_0 + b_1 x_1^* + \cdots + b_k x_k^*\right) = \sum_{i,j=0}^{k} x_i^* x_j^* Cov(b_i, b_j) \ where\ x_0^* = 1$$

4. Covariance (g,z) will be calculated using the formula:

$$\mathrm{Cov}(g, z) = \mathrm{Cov}\left(\gamma, b_0 + b_1 x_1^* + \cdots + b_k x_k^*\right) = \sum_{i=0}^{k} x_i^* Cov(\gamma, b_i)$$

Then VarTheta is equal to $\begin{pmatrix} Var(g) & Cov(g,z) \\ Cov(g,z) & Var(z) \end{pmatrix}$

15.1.3.3. Computation of the final confidence interval with missing data method (NRI+MI) (STEP 4 details)

STEPS 1 and 2 are repeated on each imputed dataset produced by the multiple imputation method (fixed to 1000 datasets).

Estimated risk difference ($RD_{estimated}$) per imputed datasets is calculated using STEP 1.

Using Lower and Upper bounds calculated with Reeve's method per imputed datasets in STEP 2, and assuming that risk difference is normally distributed, the estimated standard error ($SE_{estimated}$) is calculated as:

SE_{low}= ($RD_{estimated}$ – Lower Bound) / ($z_{\alpha/2}$)

SE_{up}= (Upper bound - $RD_{estimated}$) / ($z_{\alpha/2}$)

Where $z_{\alpha/2}$=1.96 for 95% CI bounds

$SE_{estimated}$ = mean (SE_{up}, SE_{low}).

The couple ($RD_{estimated}$, $SE_{estimated}$) per imputed dataset is then combine using Rubin's Rules to produce the final confidence interval.

The following SAS code will be used to combine the results:

```
proc mianalyze data=data_RD_SE_per_MI_dataset;
      modeleffects RD_ESTIMATE;
      stderr RD_SE;
run;
```

15.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

As sensitivity analysis, the primary endpoint will also be analyzed on the PPS with the combination of NRI and MI methods as the missing data method (described in section 15.1.2.4) using M1 as for the primary analysis.

15.2. SECONDARY EFFICACY

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. PASI 75

The proportion of patients with a PASI 75 response will be assessed at Week 24.

The derivation of PASI 75 is detailed in section 15.1.1.

15.2.1.2. Improvement in PASI

The mean percentage improvement in PASI at Week 16 will be assessed.

15.2.1.3. sPGA

The proportion of patients with a sPGA ≤ 1 (clear or almost clear) at Week 16 will be assessed.

15.2.1.4. DLQI

The proportion of patients achieving a DLQI of 0 or 1 at Week 16 will be assessed.

15.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE(S)

Missing PASI 75 at Week 24 as well as missing sPGA and DLQI at Week 16 will be imputed using the combination of NRI and LOCF methods as missing data method considering NRI at Week 24 or Week 16 according to the variable considered (see Section 15.1.2.4).

15.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

All secondary analyses will be based on FAS.

15.2.3.1. PASI 75, sPGA and DLQI analysis

The risk difference will be estimated using the method of Reeve with a 95% significance level (see Section 15.1.3).

15.2.3.2. Improvement in PASI

For the percentage improvement from baseline in PASI, analysis of covariance (ANCOVA) will be used, comparing the mean percentage improvement from Baseline of PASI between BI 695501 versus US-licensed Humira at Week 16. The estimate of the difference will be computed with its 95% CI.

ANCOVA will be performed based on the following model:

(M2) PASI percentage improvement from baseline at Week 16 = Treatment + Baseline PASI + Prior exposure to a biologic agent + random error

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF for overall and Period 1 outputs.

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 objective in this trial.

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

Other safety endpoints are:

- Proportion of patients with AEs, SAEs, and AESIs

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 19.1 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.

16.1.1. ADVERSE EVENT SPECIFIC DERIVATION

16.1.1.1. Treatment Emergent Adverse Event

Treatment-Emergent Adverse Events (TEAEs) are defined as AEs that started or worsened on or after the first dose of trial medication and prior to the last date of trial medication + 10 weeks (70 days) inclusive.

There is one specific period of interest:

- Period 1 starts on the first administration day (Day 1 visit) and finishes prior to the visit date of Day 113 visit.

Period 1 Treatment-Emergent Adverse Events (P1 TEAEs) are defined as AEs that started or worsened on or after the first dose of trial medication during period 1 and prior to or at the last date of trial medication during period 1 + 10 weeks (70 days) inclusive.

Non-TEAEs will be classified as “Screening” if AE start date is strictly prior the first injection date. Non-TEAEs will

be classified as “Post treatment” if AE start date is strictly after the last injection date + 70 days.

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.

16.1.1.2. Risk ratio

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

Risk ratio will be defined as: [a/(a+b)]/[c/(c+d)]

where:

1. **a** is the number of subjects with AESI within treatment group BI 695501
2. **a+b** is the total number of subjects in treatment group BI 695501
3. **c** is the number of subjects with AESI within treatment Humira
4. **c+d** is the total number of subjects in treatment group Humira

PROC FREQ with option RELRISK will be used for programming purpose.

```
proc freq data=data_AESI;
      tables AESI_WITH_CRITERION*TRT;
      exact relrisk(method=score);
      weight count;
run;
```

16.1.2. ALL TEAEs

Number of subjects, percentages, and number of events overall and for period 1 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.

16.1.2.1. Intensity

Intensity is classed as mild/ moderate/ severe (increasing intensity). TEAEs starting after the first dose of trial medication 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.

16.1.2.2. 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.

16.1.3. 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 overall and for period 1 by SOC and PT.

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

16.1.4. 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 overall and for period 1 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 overall and for period 1.

A summary of related SAEs by SOC and PT will also be prepared overall and for period 1.

The SAEs and Non-SAEs will be listed.

16.1.5. Adverse Events Leading to Death

TEAEs leading to Death are those events which 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.

16.1.6. 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	√	√

16.1.6.1. 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.

16.1.6.2. 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.

16.1.6.3. 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.

16.1.6.4. 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 16.3.1)

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.

16.1.6.5. 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.

16.1.6.6. 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.

16.1.7. 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.

16.2. 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.

16.3. 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 5.

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 trial medication up to the end of a period (i.e. up to 10 weeks after the last dose of the trial medication) will be assigned to the treatment phase for evaluation. Moreover, tables about DILI 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.

16.3.1. 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):

1. Normal liver function at Baseline is defined as AST and ALT and Total Bilirubin values measured

at baseline are each <= respective ULN.

2. Impaired liver function tests at Baseline is defined as AST or ALT or Total Bilirubin values measured at baseline is > respective ULN.

3. For post baseline visits:

    1. Category 1: Subject with normal liver function at Baseline and (AST and/or ALT ≥3 times ULN and TBL ≥2 times ULN within the same sample).

    2. Category 2: Subject with impaired liver function at Baseline and (AST and/or ALT ≥3 times the Baseline value and TBL ≥2 times the Baseline value within the same sample.).

    3. Category 3: marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

16.3.2. 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.

16.3.3. OTHER SAFETY LABORATORY EVALUATIONS

16.3.3.1. Pregnancy test

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

The pregnancy results will be listed as well.

16.3.3.2. Tuberculosis test

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

The TB test results will be listed as well.

16.4. 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.

16.5. 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 (^{o}C). Conversion: Temperature(°C)=[Temperature (F)-32]/1.8

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.

16.6. 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. REFERENCES

ICH E9 – Statistical Principles for Clinical Trials (Issued 1998)

Reeve Russel (2016) Confidence interval of difference of proportions in logistic regression in presence of covariates. Statistical Methods in Medical Research. DOI : 10.1177/0962280216631583

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Output Conventions

File names should only consist of lowercase letters, digits (0 to 9) and hyphens. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

The program, program log and output file name should reflect the type of the statistical output. The output files will contain the output number in addition. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('t' for table, 'l' for listing and 'f' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (eg t-14-3-01-1.RTF)

As far as possible, output files should be in RTF format.

The outputs will be provided in pdf format.

Paper Size, Orientation and Margins

The size of paper will be Letter.

The page orientation should preferably be landscape, but portrait is also permitted.

Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.

The number of columns per page (linesize) should 134 for Letter.

The number of rows per page (pagesize) should be 40 for Letter.

FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No bolding, underlining italics or subscripting should be permitted. Try to avoid using superscripts, unless absolutely necessary. Single spacing should be used for all text.

Figures should have a default font of "Times Roman", "Helvetica", or "Courier New".

This can be achieved by using the following options in SAS:

```
goptions
gunit = pct
cback = white
colors = (black)
hby = 2.4
```

ftext = “TimesRoman”
htext = 2.5;

HEADER INFORMATION

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
- The customer name and protocol number should appear in row 1, left-aligned
- The output identification number should appear in row 2, left-aligned
- The output title should start in row 2 after output identification number separated by a double dot, left-aligned
- The output population should appear in row 2 after output title separated by a dash, left-aligned. The population should not be spelled out in full, e.g. FAS in preference to Full analysis set.
- Row 3 should be a continuous row of underscores (‘_’) (the number of underscores should equal the linesize)
- Row 4 should be a blank line
- Mixed case should be used for titles
- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (e.g., Vital Signs) followed by metric (e.g., Change from Baseline) e.g. Vital Signs – Change from Baseline.
- Titles should not contain quotation marks or footnote references
- The column headings should be underlined with a row of underscores (‘_’)
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered
- Column headings containing numbers should be centered
- Column headings should be in sentence case
- In general, the population count should appear in the column header in the form “(N=XXX)”
- “Statistic” should be the column header over n, Mean, SE, n (%) etc.
- As a rule, all columns should have column headings.

TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank
- The left hand column should start in column 1. No indenting or centering of the output should occur.

- Rounding should be done with the SAS function ROUND, if no further specification.
- Numbers in tables should be rounded, not truncated, if no further specification.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- The trial drug should appear first in tables with treatments as columns
- In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization.
- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).
- Do not use superscripts and subscripts
- The width of the entire output should match the linesize option

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, IQR, Minimum, Maximum or n, gMean, gCV, Mean, CV, SD, Median, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum and maximum: N
  - Mean, gMean, median, gCV% and CV%: N + 1
  - SD, IQR: N + 2

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

77 (100.0%)
50 (64.9%)
0 (0.0%)

- Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1%

will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.

E.g., (<0.1%)
(6.8%)
(>99.9%)

- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

- As a rule confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence intervals should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:

(-0.12, -0.10)
(9.54, 12.91)

P-values:

- P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values

- A "0" should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in an end-of-text table or subject listing.

FIGURE OUTPUT CONVENTIONS

- Figures will be provided in PDF files using the SAS Output Delivery System (ODS) as generated by SAS.
- The image should be clear and of high quality when viewed in the Word document, and when printed.
- In general, boxes around the figures should be used.

FOOTNOTE INFORMATION

Footers should be defined as follows:

- A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page
- Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table
- The program path and name and version number (if applicable) should appear as footnote 1 at the bottom of the page
- The date/time stamp should appear as footnote 2 at the bottom of the page
- Footnotes should be left-aligned.
- Footnotes should be in sentence case.
- Only "typewriter" symbols are permitted – e.g., "*", "$", "#", "@", "&" and "+".
- The choice of footnote symbols should be consistent. E.g., if you have the footnote "# indicates last observation carried forward" for one table, the same symbol and footnote should indicate LOCF for all tables.
- If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.
- The page identification in the format Page X of Y (where Y is the total number of pages for the output) should appear in the footer, right aligned.

Ordering of footnotes should be as follows:

1.) Source data listing reference, if necessary
2.) Abbreviations and definitions
3.) Formulae
4.) P-value significance footnote
5.) Symbols
6.) Specific notes

- Common notes from table to table should appear in the same order.

The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English US.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables and Graphs
BI 695501	BI 695501
US-licensed Humira®	Humira

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name	Visits as per protocol
Day -28 to -1	D-28 to -1	
Day 1	D1	Baseline
Day 8	D8	Day 8 (Week 1)
…	…	…
Day 232	D232	….

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- randomized treatment group (or treatment received if it's a safety output)
- center-subject ID
- date including Study Day (where applicable),
- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

The visit as recorded in the eCRF will be displayed in the listings (and not the remapped visit).

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR PRIOR / ACTIVE MEDICAL HISTORY, SURGERIES AND PROCEDURES

Partial date to be imputed as:

Start date	Earliest possible date	first day of month if day unknown or 1st January if day and month are unknown
Stop date	Latest possible date	last day of month if day unknown or 31st December if day and month are unknown, if not resulting in a date later than the date of subject's death. In the later case the date of death will be used for imputation.

General rules:

If stop date < trial med start date, assign as prior
If stop date >= trial med start date and start date <= end of treatment, assign as concomitant
If stop date >= trial med start date and start date > end of treatment, assign as post Treatment

If Missing stop date: (Rules 2)

If stop date is missing could never be assumed as prior
If start date <= end of treatment, assign as concomitant
If start date > end of treatment, assign as post treatment

If Missing Start date: (Rules 3)

If stop date < trial med start date, assign as prior
If stop date >= trial med start date, assign as active
Cannot be assigned as 'post treatment'

START DATE	STOP DATE	ACTION
Known	Known	General rules
	Partial	General rules
	Missing	Rules 2
Partial	Known	General rules
	Partial	General rules
	Missing	Rules 2

START DATE	STOP DATE	ACTION
Missing	Known	Rules 3
	Partial	Rules 3
	Missing	Assign as concomitant

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known Partial Missing	If start date < trial med start date or start date> trial med stop date +70 days, then not TEAE If start date >= trial med start date and start date <= trial med stop date +70 days, then TEAE
Partial, but known components show that it cannot be on or after trial med start date	Known Partial Missing	Not TEAE
Partial, could be on or after trial med start date	Known	Impute start date as earliest possible date, (i.e., first day of month if day unknown or 1st January if day and month are unknown), except if only day is missing and month and year of start date are the same as for trial med start date or if day and month are missing and year of start date is the same as for trial med start date. In the later cases, the trial med start date will be used for the imputation. If start date <= stop date, then: If stop date < trial med start date, then not TEAE If start date > trial med end date +70 days, then not TEAE If stop date >= trial med start date and start date <= trial med end date +70 days, then TEAE If start date > stop date, then: Consider the start date as Missing and apply the algorithms for missing start date
	Partial	Impute start date as above. Impute stop date as latest possible date (i.e., last day of month

START DATE	STOP DATE	ACTION
		if day unknown or 31st December if day and month are unknown), if not resulting in a date later than the date of subject's death. In the later case the date of death will be used for imputation. If start date <= stop date, then: If stop date < trial med start date, then not TEAE If start date > trial med end date +70 days, then not TEAE If stop date >= trial med start date and start date <= trial med end date +70 days, then TEAE If start date > stop date, then: Consider the start and stop dates as Missing and apply the algorithms for missing start date
	Missing	Assumed TEAE
Missing	Known	If stop date < trial med start date, then not TEAE If stop date >= trial med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < trial med start date, then not TEAE If stop date >= trial med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

Partial date to be imputed as:

Start date	Earliest possible date	first day of month if day unknown or 1st January if day and month are unknown
Stop date	Latest possible date	last day of month if day unknown or 31st December if day and month are unknown, if not resulting in a date later than the date of subject's death. In the later case the date of

		death will be used for imputation.

General rules:

If stop date < trial med start date, assign as prior
If stop date >= trial med start date and start date <= end of treatment, assign as concomitant
If stop date >= trial med start date and start date > end of treatment, assign as post Treatment

If Missing stop date: (Rules 2)

If stop date is missing could never be assumed a prior medication
If start date <= end of treatment, assign as concomitant
If start date > end of treatment, assign as post treatment

If Missing Start date: (Rules 3)

If stop date < trial med start date, assign as prior
If stop date >= trial med start date, assign as concomitant
Cannot be assigned as 'post treatment'

START DATE	STOP DATE	ACTION
Known	Known	General rules
	Partial	General rules
	Missing	Rules 2
Partial	Known	General rules
	Partial	General rules
	Missing	Rules 2
Missing	Known	Rules 3
	Partial	Rules 3
	Missing	Assign as concomitant

APPENDIX 3. **EMA SOC ORDER FOR PRESENTATION OF THE AE IN THE TABLES.**

Order	System Organ Class
0	Uncoded
1	Infections and infestations
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3	Blood and lymphatic system disorders
4	Immune system disorders
5	Endocrine disorders
6	Metabolism and nutrition disorders
7	Psychiatric disorders
8	Nervous system disorders
9	Eye disorders
10	Ear and labyrinth disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
14	Gastrointestinal disorders
15	Hepatobiliary disorders
16	Skin and subcutaneous tissue disorders
17	Musculoskeletal and connective tissue disorders
18	Renal and urinary disorders
19	Pregnancy, puerperium and perinatal conditions
20	Reproductive system and breast disorders
21	Congenital, familial and genetic disorders
22	General disorders and administration site conditions
23	Investigations
24	Injury, poisoning and procedural complications
25	Surgical and medical procedures
26	Social circumstances
27	Product issues

APPENDIX 4. FILES ATTACHED TO SAP

Current BIcMQs Administration site reaction

Cut-off implementation document: BI1297_12_cut_off_v1.3_19SEP2017

APPENDIX 5. LABORATORY ASSESSMENTS

Laboratory parameter	SI unit	US unit
Serum chemistry		
Creatinine	umol/L	mg/dL
Alkaline phosphatase	IU/L	IU/L
Aspartate aminotransferase (AST)	IU/L	IU/L
Alanine aminotransferase (ALT)	IU/L	IU/L
Gamma glutamyl transpeptidase (GGT)	IU/L	IU/L
Total bilirubin	umol/L	mg/dL
Direct bilirubin	umol/L	mg/dL
Glucose	mmol/L	mg/dL
Total cholesterol	mmol/L	mg/dL
Total protein	g/L	g/dL
Sodium	mmol/L	mEq/L
Potassium	mmol/L	mEq/L
Chloride	mmol/L	mEq/L
Calcium	mmol/L	mg/dL
Albumin	g/L	g/dL
Hematology		
Hemoglobin	g/L	g/dL
Hematocrit	V/V	%
Erythrocyte	10^12/L	10^6/uL
Platelets	10^9/L	10^3/uL
White blood cells	10^9/L	10^3/uL
Lymphocytes	10^9/L	10^3/uL
Neutrophils	10^9/L	10^3/uL
Urinalysis		
Protein	g/L	g/dL
Glucose	mmol/L	mg/dL
Blood	N/A	N/A

APPENDIX 6. SAS CODE FOR DIFFERENCE IN PROPORTION CIS

```
%let K=1000000;/*number of simulation*/
%let alpha=0.05;/*confidence level*/

proc IML;
      /*create theta and vartheta*/
      theta={&G. &Z.}; print theta; /*create theta vector*/
      vartheta={&VARG. &COVGZ. , &COVGZ. &VARZ.}; print vartheta; /*create
vartheta vector*/

      /*Create Xc the cholesky decomposition of Vartheta*/
      Xc = t(root(Vartheta));

      /*create X random normal vector*/
      call randseed(456); /* set random number seed */
      X = j(&K.,2);  /* allocate the X vector */
      call randgen(X,"Normal");

      /*Write X matrix in a sas dataset called X*/
      X1=X[,1];
      X2=X[,2];
      create X var{X1 X2};
      append;
      close X;

      /*Calculate Y = X %% Xc*/
      Y=X*Xc;

      /*G,Z*/
      G=Y[,1]+Theta[1,1];
      Z=Y[,2]+Theta[1,2];
      DELTA=(1/(1+exp(-(G+Z))))-(1/(1+exp(-Z)));
      call sort(DELTA);

      LOW=DELTA[round(&k.*(&alpha./2))]; print low;
      UP=DELTA[&K.-round(&k.*(&alpha./2))]; print up;

quit;
```