STATISTICAL ANALYSIS PLAN

1297.4

BI 695501 VERSUS HUMIRA® IN PATIENTS WITH ACTIVE CROHN'S DISEASE: A RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PARALLEL GROUP, EXPLORATORY TRIAL COMPARING EFFICACY, ENDOSCOPIC IMPROVEMENT, SAFETY, AND IMMUNOGENICITY

AUTHOR:
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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan FINAL V4.0 (Dated 22MAY2019) for Protocol 1297.4.

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OUTPUT TEMPLATES SIGNATURE PAGE

Please refer to Output Templates Final V2.0 (Dated 22MAY2019) for Protocol 1297.4.

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Final Version 1.1	24MAY2018		Update Periods per BI Request and minor text edits
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Final Version 3.0	29NOV2018		Update versioning to 3.0 before signatures
Final Version 4.0	22MAY2019		Update Section 5.4 – Per Protocol Analysis Set [PPS] for more clarity on the 2 Per Protocol Sets Update of PK measurement time points

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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 1297.4. 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 Final Protocol, Protocol Version 3.0 (Revised Protocol (based on global amendment 2)), dated 12th of December 2017.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this trial is to compare the clinical efficacy of BI 695501 with EU-approved Humira® in patients with active Crohn's disease (CD).

2.2. SECONDARY OBJECTIVES

The secondary objectives of this trial are to compare the efficacy and safety of BI 695501 with EU-approved Humira across the induction and maintenance phases, as covered by Crohn's disease activity index (CDAI) and safety monitoring.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is an exploratory, randomized, 56-week, double-blind, parallel arm, multiple dose, active comparator trial of BI 695501 and EU-approved Humira, with a 48-week treatment period and a 10-week follow-up period (starting after last dose of trial medication at Week 46) in patients with moderately to severely active CD, and a primary endpoint assessment at Week 4.

Approximately 130 patients with moderately to severely active CD, for more than 4 months will be randomized into the trial.

The trial will consist of a Screening period of up to a maximum of 28 days and a 48-week treatment period. The treatment period will consist of an induction period from Baseline to Week 4, a maintenance period from Week 5 to Week 48, and a 10-week safety follow-up period (starting after last dose of trial medication at Week 46).

At Week 4, patients with clinical response will be assessed and only patients who are classified as responders (CDAI decrease of ≥70 compared to baseline) will continue on trial and enter the maintenance phase. Patients who are originally randomized to EU-approved Humira will switch to BI 695501 at Week 24.

Patients will undergo up to 27 visits (including 13 trial medication administration only visits) over the duration of the trial (56 weeks). Every effort should be made for all patients who complete the total 48-week treatment period or who discontinue the trial medication early, to return for a Safety Follow-up Visit 10 weeks after their last dose of trial medication.

Trial medication will be administered by subcutaneous (s.c.) injection.

Diagram of trial design

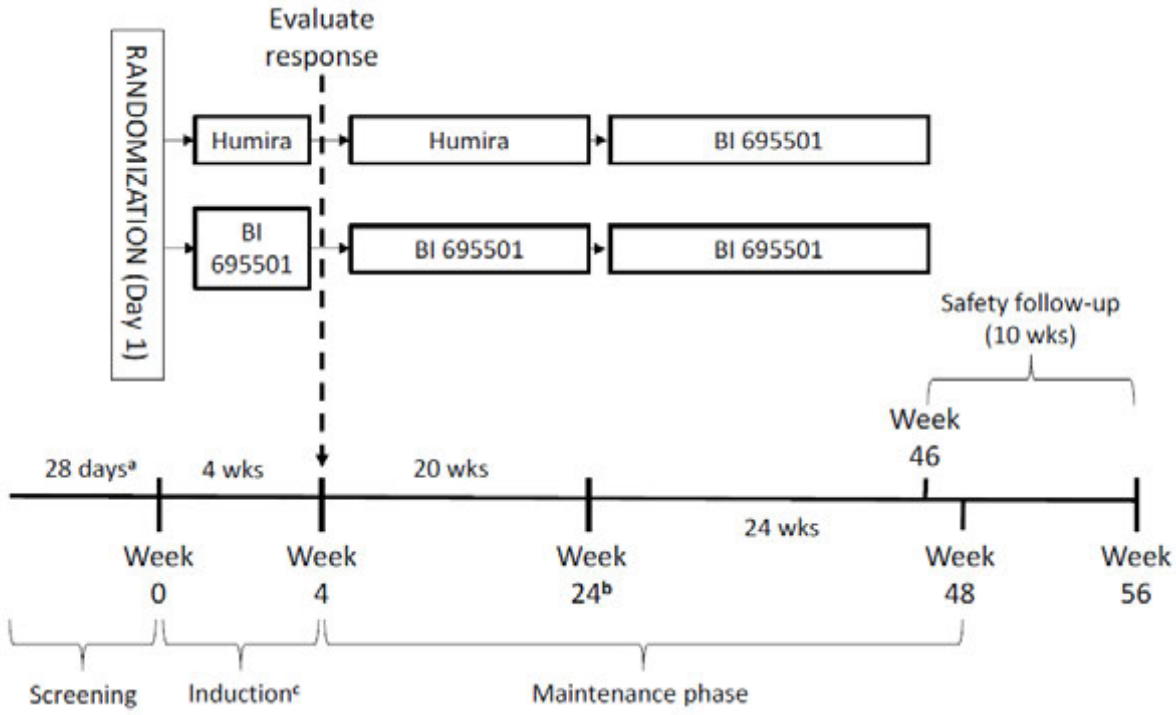

Figure 3.1: 1 Overview of trial design

wks: weeks.
Note: In the figure, Humira represents EU-approved Humira.

a Screening period of 28 days to include 2 visits (Visit 1 during the period Day -28 to Day -14 and Visit 1.1 on Day -9 ± 2 days).

b At Week 24, patients initially randomized to EU-approved Humira will switch to receive BI 695501 for the remainder of the treatment period.

c Induction phase will comprise the following doses of trial medication: a loading dose of 160 mg on Day 1 and a second dose of 80 mg at Week 2 (Day 15). Evaluation of clinical response will be performed at the Week 4 visit and only responders will continue in the trial.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Sections "FLOW CHART A: SCREENING AND INDUCTION PERIOD" and "FLOW CHART B: MAINTENANCE PERIOD" of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

No change to analysis from protocol is planned.

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 all primary efficacy endpoint data are available and cleaned (i.e., approximately 4 weeks after the last patient has been randomized). The cut-off date will be the date on which the last patient completes the Week 4 visit and will be the same for all patients. A database snapshot will be taken with regard to this cut-off date; it will include data available in the database up to and including the cut-off date of Week 4 visit and will be used for performing the analysis (please refer to APPENDIX 4). Only cumulative 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. Only a selected team, not involved in any other trial activities, will have access to the unblinded snapshot data and will be required to sign a confidentiality agreement. Efficacy data and all available data for safety and other endpoints will be included up to the Week 4 visit only.
To ensure that the data integrity of the continuing trial will not be violated, a charter will be prepared in advance, outlining the procedures to be followed. This document will describe the measures to be implemented by the Sponsor to protect the integrity of the trial until the final database lock. Team members involved in the conduct of the trial as well as the site personnel and patients will remain blinded until the final database lock. A separate clinical trial report (CTR) will not be prepared for this analysis; rather it will be attached to the final CTR.

4.2. FINAL ANALYSIS

A final analysis (including all endpoints) will be performed when all trial data are available, i.e., approximately

56 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 and efficacy endpoints collected until Week 56. 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 of the dedicated staff for primary analysis (Week 4), and unblinding for final analysis (Week 56). The analysis sets will be checked at the time of final analysis and may be updated according to data entered in the database at the time of database lock.

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 CDAI, measured at baseline and at least once post-baseline (on Week 4).

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. Two Per Protocol Analysis Sets will be analyzed. One PPS for the Primary Analysis based on the week 4 data

(primary efficacy endpoint) (PPS) and one for the Final Analysis based on the week 24 data (secondary efficacy endpoint) (PPS2).

The important protocol violations 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. Defined as, on the patient level, at least one kit number used before Week 4 – for Primary Analysis PPS – and before Week 24 – for Final Analysis PPS – does not correspond to the initial randomized treatment group.

- Important violation of treatment compliance prior to Week 4 – for Primary Analysis PPS – and prior to Week 24 – for Final Analysis PPS: medical team will review subjects with treatment compliance outside 80% and 120% (refer to section 14.1) and decide if the violation is severe.

- Important violation of inclusion/exclusion criteria
    - IC1
    - IC2
    - EC1
    - EC7
    - EC8
    - EC9
    - EC10
    - EC14
    - EC21
    - EC25
    - EC27
    - EC28

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 (full or partial) 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

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 study 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). 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 acceptable timeframe 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.

Treatment early termination data will be included in 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

The default significance level will be 10%; confidence intervals will be 90% and 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 versus EU-approved Humira)
- Prior exposure to infliximab (Yes/No).
- Baseline SES-CD (<16 or ≥16)

7.2. MULTICENTER STUDIES

This trial will be conducted by multiple investigators at multiple centers internationally, approximately 128 clinical sites across approximately 13 countries. Randomization to treatment arms is stratified by prior exposure to infliximab (Yes/No) and screening SES-CD (<16 or ≥16). 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

There is no examination of subgroups.

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, PPS2)
- 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
- Screen failure (defined as withdrawn from trial prior to randomization)
- Primary reason for non-inclusion
- Randomized
- Randomized but not treated
- Treated
- Subjects with CDAI decrease ≥ 70 at Day 29 (Week 4)
- Subjects treated after Day 29 (Week 4)
- Completed treatment at Day 337 (Week 48)
- Completed the trial per the protocol
- Discontinued from treatment strictly before Day 29 (Week 4), primary reason for premature discontinuation from treatment before Day 29 (Week 4)
- Discontinued from treatment (before Week 48), primary reason for premature discontinuation from treatment
- Discontinued from trial (after Week 48), primary reason for premature discontinuation from trial

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

- Screened
- Screen failure (defined as withdrawn from trial prior to randomization)
- Randomized
- Randomized but not treated

- Treated
- Subjects with CDAI decrease ≥ 70 at Day 29 (Week 4)
- Subjects treated after Day 29 (Week 4)
- Completed treatment at Day 337 (Week 48)
- Completed the trial (Week 56)

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.

Important protocol violations are defined as:

- entering the study even though the subject did not fulfill 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 the ones excluding subjects from either one of the PPSs (refer to section 5.4).

The full protocol deviations log will be attached to the clinical trial 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 and SAF, and at Final Analysis for RND, FAS, PPS, PPS2 and SAF:

- Age (years) at Informed Consent
- Gender (Male/Female)

- Childbearing potential (Post-Menopausal/Surgically Sterile/Childbearing Potential (tubal ligation at least 6 weeks before screening is considered not of childbearing potential)
- 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 infliximab Yes/No, screening SES-CD <16/≥16) based on eCRF data, will be presented at Primary and Final Analyses for the FAS. Any differences between stratification data in the eCRF and IVRS will be documented.

The following baseline disease characteristics will be presented at Primary Analysis for the FAS, PPS, SAF, and at Final Analysis for FAS, PPS2, and SAF:

- CDAI score at baseline as collected in the eCRF
- Mucosal ulceration at baseline as collected in the SES-CD under the item: Extent of ulcerated surface subscore. The second reading will be taken into account in case there were two readings.

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
- CRP at baseline
- Fecal calprotectin at baseline

- Stool studies at baseline (*Salmonella, Shigella, Yersinia, Campylobacter, Vibrio, Escherichia coli* O157/H7*, Clostridium difficile* toxin*,* Enteric parasites and their ova *including Cryptosporidia*), and other identified pathogens.

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
- Age (years) = (date of consent– date of birth)/365.25

11. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History information will be presented at Primary Analysis for the SAF, and at Final Analysis for the FAS 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 (System Organ Class) 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.

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

12. MEDICATIONS

Medications will be presented at Primary Analysis for the SAF, at Final Analysis for the FAS and SAF. They will be coded using the WHO Drug Dictionary (WHO-DD) 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.

Prior, concomitant, and post medications will be presented in separate tables.

13. TRIAL MEDICATION EXPOSURE

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

SAF.

The proportion of subjects treated at each planned visit (administration on Day 1 and every other week until Day 323) and per treatment group will be presented.

Descriptive statistics for the number of injections from Day 1 up to Week 4 (included) and from Week 4 (excluded) up to Week 46 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, ≥ 24 weeks, ≥ 48 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 subject/365.25.

14. STUDY MEDICATION COMPLIANCE

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

Compliance (%) = 100% if the injection occurred at the specific visit

= 0% otherwise

Note: One administration is planned at each visit.

- "Overall" compliance will be calculated as follows:

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

- "Week 4" compliance will be calculated considering the injections until Week 4 (visit 4) (included).
- "Week 24" compliance will be calculated considering the injections until Week 24 (visit 14) (included).

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy endpoint is:

- The proportion of patients in each treatment group with a clinical response (CDAI decrease of ≥70 compared with baseline) at Week 4

CDAI decrease at Week 4 is assessed as the decrease relative to baseline measurement:

- Decrease = CDAI at Baseline - CDAI at Week 4

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

Subjects with a decrease greater or equal to 70 are responders. Other subjects are considered as non-responders.

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

No missing data for the primary analysis endpoint are expected for the FAS, because Week 4 is the first post-baseline visit for efficacy assessment and, in case of discontinuation prior to Week 4, the EoT efficacy assessments should be performed.

The non-responder imputation principle will be followed for the FAS. CDAI evaluation will be set to non-

responder at Week 4 if the subject:

- discontinues treatment prior to Week 4
- is lost-to-follow-up (according to eCRF record for “End of Treatment” or “Trial Completion”) prior to Week 4

15.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary efficacy analysis will be performed for the FAS. Patients will be assigned to the treatment they were randomized to receive.

The primary objective of this trial is to compare the clinical efficacy of BI 695501 with EU-approved Humira in patients with active CD at the end of the induction phase at Week 4 by means of the Relative Risk (RR).

The primary analysis of the observed proportion of patients with a clinical response (CDAI decrease of ≥70 compared with baseline) at Week 4 will be based on log-linked binomial model.

The statistical model can be described as follows:

- (M1) Response to treatment at Week 4 = treatment + prior infliximab exposure + screening SES-CD

This model includes the stratification factor, prior exposure to infliximab, and treatment as fixed effects and screening SES-CD will be included as a categorical effect:

- Treatment (BI 695501, EU-approved Humira)
- Prior exposure to infliximab (Yes/No)
- Screening SES-CD (<16 or ≥16)

The relative risk estimate together with its 90% and 95% CI (ratio scale) will be produced. The following SAS code will be used:

```
proc genmod data=data_CDAI70 descend;
      class CDAI70(ref="N") TRTP(ref="HUMIRA") EXP_PRIO(ref=”N”) BAS_SES
      (ref=”<16”) / param=GLM;
      model CDAI70=TRTP EXP_PRIO SCR_SES/ dist=binomial link=logit;
      lsmeans TRT / ilink;
run;
```

15.2. SECONDARY EFFICACY

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

The following parameters are based on an imputation of CDAI described in Section 15.2.2:

15.2.1.1. CDAI clinical response

The proportion of patients in each treatment group with a clinical response (CDAI decrease of ≥70 compared with baseline) will be assessed at Week 24.

The derivation of CDAI decrease is detailed in section 15.1.1. Subjects with a decrease greater or equal to 70 are responders. Other subjects are considered as non-responders.

In addition, RR and risk difference together with 90% and 95% CIs will be presented.

15.2.1.2. CDAI clinical remission

The proportion of patients in each treatment group in clinical remission (CDAI <150) will be assessed at Week 24.

Subjects with CDAI <150 at Week 24 will be considered as clinical remission cases.

In addition, RR and risk difference together with 90% and 95% CIs will be presented.

15.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE

Missing CDAI at Week 24 will be imputed using the combination of NRI and LOCF methods. Only the data up to Week 24, 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 secondary analysis on the FAS

	prior to/on Week 24	
Secondary analysis (FAS)	Discontinued treatment[#]	Did NOT discontinue treatment
CDAI computable using observed data at Week 24	Observed	Observed
CDAI NOT computable using observed data at Week 24	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:

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

STEP 2:
NRI principle will be considered at Week 24 as detailed in section 15.1.2.

15.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

Secondary efficacy endpoints will be presented with descriptive statistics for FAS and PPS2. The relative risk of the proportions will be computed and presented together with its 90% and 95% CI and risk difference and interpreted in a descriptive manner.

16. SAFETY OUTCOMES

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

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 endpoints considered as secondary endpoints are defined as:

- Proportion of patients with AEs, SAEs, and AESIs (e.g., serious infections)
- Proportion of patients with infections/serious infections (seriousness of infection defined as requirement of i.v. antibiotics for treatment and/or meeting seriousness criteria to be qualified as an SAE)
- Proportion of patients who experience hypersensitivity reactions
- Proportion of patients who experience DILI (Drug Induced Liver Injury)
- Proportion of patients with injection-site reactions

Another safety endpoint is the proportion of patients who discontinue due to drug-related AEs and AESIs (e.g., serious infections and allergic reactions).

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 19.1 or higher. The SOCs will be sorted by internationally agreed EMA SOC order (refer to APPENDIX 3); PTs 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 intensity, 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 are two specific periods of interest:

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 and prior to the date of Week 24 visit or within 10 weeks (70 days, inclusive) after the last dose of IMP for patients who discontinued the treatment before Week 24.

Period 2 Treatment-Emergent Adverse Events (P2 TEAEs) are defined as AEs that started or worsened on Week 24 visit and prior to or on the Week 56 visit or within 10 weeks (70 days, inclusive) after the last dose of IMP for patients discontinuing treatment prior to Week 46.

Non-TEAEs will be classified as "Screening" if AE start date is strictly prior to 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 all adverse events.

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

where:

- **a** is the number of subjects with AE within treatment group BI 695501
- **a+b** is the total number of subjects in treatment group BI 695501
- **c** is the number of subjects with AE within treatment Humira
- **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;
      tables trt*ae_overall;
      exact relrisk(method=score);
      weight count;
run;
```

16.1.1.3. Risk difference

The risk difference between both treatment groups will be displayed together with its 95% confidence interval (CI) using the same SAS code as in section 16.1.1.2.

16.1.2. ALL TEAEs

Number of subjects, percentages, and number of events overall and for period 1 and period 2 will be presented by SOC and PT and also broken down further by maximum intensity and relationship to trial medication.

Periods for TEAE's:

Period 1	Visit date within • [first injection date; Week 24 Visit] or • [first injection date; last injection date + 10 weeks (70 days)] (for patients that discontinued the treatment before week 24)].
Period 2	Visit date within • [Week 24 Visit; Week 56 Visit[or • [Week 24 visit; last injection date + 10 weeks (70 days)] (for patients that discontinued the treatment before week 56)].

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 intensity 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 intensity 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 and at least 1 episode was assessed as related, the TEAE will be regarded as related in the corresponding relationship summaries.

All drug related AEs will be listed.

In addition, the number and percentages of subjects who discontinue due to drug-related TEAEs will be prepared

overall by SOC and PT.

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 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 including the number of subjects, percentages and number of events.

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

The SAEs and Non-SAEs will be listed.

16.1.5. Non-Serious Adverse 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.

16.1.6. 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.

16.1.7. 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.

In addition, the number and percentages of subjects who discontinue due to drug-related AESI (as reported by investigators and CTP specified) will be prepared overall 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	√	√
Infections		√
Hypersensitivity reactions	√	√
Drug induced liver injury	√	√
Injection site reactions		√
Anaphylactic reactions	√	√

16.1.7.1. 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.

16.1.7.2. Infections and 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.

16.1.7.3. 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.

16.1.7.4. 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).

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.

16.1.7.5. 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

These will be presented by period and treatment.

There are 2 periods:

Period 1	Visit date within [first injection date; Week 24 Visit[+10 weeks (70 days) inclusive (for patients that discontinued the treatment before week 24).
Period 2	Visit date within • [Week 24 Visit; Week 56 Visit[or • [Week 24 visit; last injection date + 10 weeks (70 days)] (for patients that discontinued the treatment before week 56)].

Injection-site reactions will be listed.

16.1.7.6. 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.

16.1.8. 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 “Progressive Disease”.

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 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. 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 alanine aminotransferase (ALT), aspartate aminotransferase (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):
    - 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:
        - Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN for all subjects with normal liver function at baseline.

16.3.2. LABORATORY REFERENCE RANGES AND MARKEDLY 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 (°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)

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

Output File Naming 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 New 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 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
EU-approved 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 -14	D-28 to -14	
Day 1	D1	Baseline
Day 15	D15	Day 15 (Week 2)
…	…	…
Day 337	D337	….

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 latter case the date of death will be used for imputation.

General rules:

If stop date < screening date, assign as prior
If stop date >= screening date and start date <= end of treatment, assign as concomitant
If stop date >= screening 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 < screening date, assign as prior
If stop date >= screening 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

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 and prior to trial med stop date + 70 days	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 latter cases, the trial med start date will be used for the imputation.

START DATE	STOP DATE	ACTION
		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 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

START DATE	STOP DATE	ACTION
	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 latter 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

START DATE	STOP DATE	ACTION
	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 5. LABORATORY ASSESSMENTS

Laboratory parameter	SI unit	US unit
Serum chemistry		
Creatinine	umol/L	mg/dL
Alkaline phosphatase	IU/L	U/L
Aspartate aminotransferase (AST)	U/L	U/L
Alanine aminotransferase (ALT)	U/L	U/L
Gamma glutamyl transpeptidase (GGT)	U/L	U/L
Lactic dehydrogenase	U/L	U/L
Lipase	U/L	U/L
Amylase	U/L	U/L
IgE	kUL	kUL
IgG	g/L	ng/dL
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
Bicarbonate	mmol/L	nEq/L
Uric acid	umol/L	mg/dL
High density lipoprotein cholesterol	mmol/L	mg/dL
Calculated low density lipoprotein	mmol/L	mg/dL
Triglycerides	mmol/L	mg/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

Laboratory parameter	SI unit	US unit
Reticulocyte	%	%
Eosinophils	%	%
Basophils	%	%
Monocytes	%	%
Partial thromboplastin time	seconds	seconds
Prothrombin time	seconds	seconds
Fibrinogen	g/L	ng/dL
Urinalysis		
Protein	-	-
Glucose	-	-
Nitrite	-	-
Ketone	-	-
Urobilinogen	-	-
Bilirubin	-	-
Erythrocyte	-	-
Leukocyte	-	-
pH	-	-