STATISTICAL ANALYSIS PLAN

1297.3

LONG-TERM ASSESSMENT OF SAFETY, EFFICACY, PHARMACOKINETICS AND IMMUNOGENICITY OF BI 695501 IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA): AN OPEN-LABEL EXTENSION TRIAL FOR PATIENTS WHO HAVE COMPLETED TRIAL 1297.2 AND ARE ELIGIBLE FOR LONG-TERM TREATMENT WITH ADALIMUMAB

AUTHOR:

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 22JUN2016) for Protocol 1297.3.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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OUTPUT TEMPLATES SIGNATURE PAGE

Please refer to Output Templates V1.0 (Dated 22JUN2016) for Protocol 1297.3.

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety, efficacy, pharmacokinetics and immunogenicity data for Protocol 1297.3. 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 2.0, dated 19 February 2016.

2. TRIAL OBJECTIVES

The objective of this trial is to provide long-term safety, efficacy, PK, and immunogenicity data on BI 695501 administered via prefilled syringe in patients with RA who have completed Trial 1297.2.

3. TRIAL DESIGN

3.1. GENERAL DESCRIPTION

This is a single-dose, open-label trial of BI 695501 with a 48-week treatment period in patients with RA continuing to receive methotrexate (MTX) within the dose range of the 1297.2 trial for at least 12 weeks after which point the MTX dose will be at the Investigators discretion. The trial will consist of a Screening visit 14 days prior to Day 1, a 48-week treatment period and a 10-week safety follow-up period (Week 58 visit). The Screening visit will be the Week 48 visit in Trial 1297.2. Patients will undergo up to 10 visits over the duration of the trial (58 weeks).

Patients who discontinue the trial medication early (and do not withdraw consent) should return to the site for an End of Treatment (EoT) visit equivalent to the Week 48 assessments as soon as possible after last trial medication administration. For patients who discontinue treatment early, a safety follow-up visit should be performed 10 weeks after the last administration of BI 695501.

It is anticipated that approximately 300 to 400 patients with moderately to severely active RA who have completed Trial 1297.2 will be eligible and willing to participate in this extension trial. Each patient who provides informed consent and meets all the inclusion criteria and none of the exclusion criteria will self-administer 40 mg of BI 695501 every 2 weeks by subcutaneous (SC) injection.

3.2. SCHEDULE OF EVENTS

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

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

No change is planned.

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this trial.

4.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, and Sponsor Authorization of Analysis Sets.

5. ANALYSIS SETS

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

5.1. ALL SUBJECTS ENROLLED SET [ENR]

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

5.2. ALL SUBJECTS ASSIGNED SET [ASD]

The all subjects assigned (ASD) set will contain all subjects in the ENR set who were assigned to trial medication in 1297.3.

For analyses and displays based on ASD, subjects will be classified according to randomized / re-randomized treatments of trial 1297.2.

5.3. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will contain subjects from the ASD set, who received at least one dose of trial medication in Trial 1297.3, and had data recorded for at least one DAS28 (Erythrocyte Sedimentation Rate [ESR] or C-reactive protein [CRP]) or ACR20 during the 1297.3 trial (for at least one composite variable at least one non-missing value should be present on at least one post-baseline visit. It is not required that all composite variables must be non-missing at the same post-baseline visit). Subjects will be classified according to randomized / re-randomized treatments of trial 1297.2.

5.4. PER PROTOCOL ANALYSIS SET [PPAS]

No per protocol analysis set (PPAS) is defined in this trial.

5.5. SAFETY ANALYSIS SET [SAF]

The safety analysis set (SAF) will contain all subjects who received at least one dose of trial medication during the 1297.3 trial. Subjects will be classified according to randomized / re-randomized treatments received in trial 1297.2.

If there is any doubt whether a subject was treated or not, they will be assumed treated for the purposes of analysis. Subjects will be classified according to randomized / re-randomized treatments group allocated in trial 1297.2 safety outputs.

5.6. PHARMACOKINETIC FULL ANALYSIS SET [PKFS]

The pharmacokinetic full analysis set PKFS analysis set for the summary of PK concentrations consists of all subjects who receive at least one dose of trial medication and have at least one post-treatment valid PK concentration value.
The following are considered as non-valid PK concentration measurement:

- Sampling date or time missing
- Dosing date or time missing
- No valid result (NOR), No sample available (NOS), Not Analyzed (NOA)

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.

Reference start date is defined as the day of the first dose of trial medication in 1297.3 trial, (Day 1 is the day of the first dose of trial medication), or for subjects assigned to treatment but not treated it is the day of treatment assignment. This will appear in every listing where an assessment date or event date appears.

- 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, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2; Partial Date Conventions.

6.2. BASELINE

Unless otherwise specified, baseline in Trial 1297.3 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 reference start date coincide, that measurement will be considered pre-baseline. Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

For the analysis referring to the 1297.2 baseline, the baseline value as derived in 1297.2 will be used. All endpoints will be assessed using the 1297.2 baseline values. In addition, the following further endpoints will be assessed using the 1297.3 baseline values:

- DAS28 (ESR)
- ACR20 response criteria
- SF-36 v2

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, the latest available measurement within 2 days after the planned assessment will be used for by-visit summaries.

Unscheduled measurements will not be included in by-visit table summaries and by-visit graphs, but will contribute to the last observation carried forward (LOCF) values.

Treatment Early termination data will not be included in by-visit table summaries and by-visit graphs, but will contribute to the last observation carried forward (LOCF) values and be present in the listing and individual data graphs.

Listings will include all scheduled, unscheduled, retest and early discontinuation data collected in the eCRF database.

6.4. WINDOWING CONVENTIONS

Unless other 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

No formal hypothesis testing will be performed. The analysis of the data will be performed descriptively. If confidence intervals or p-values are presented, they will be interpreted in an exploratory fashion only. In this case, the default significant 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

No covariates adjustment is required in this trial.

7.2. MULTICENTER STUDIES

This trial will be conducted by multiple investigators at multiple centers internationally depending on the inclusions of trial 1297.2. No specific analyses based on (pooled) centers are planned.

Geographic region will be categorized using country information as follows:

Geographic Region	Country
Asia	Republic of Korea, Malaysia, New Zealand, Thailand
Europe (EU)	Bulgaria, Estonia, Germany, Hungary, Poland, Russian Federation, Serbia, Spain, Ukraine
Latin America	Chile
United States of America	United States

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 15.2.2 of this analysis plan.

For duration of disease and birth date, the missing date will not be imputed. Calculation for the 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

No subgroup analysis is required in this trial.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs, unless other specified within the document (e.g. plasma concentration). In particular, for presentation of results, three groups of patients will be created depending on treatments assigned in Trial 1297.2.

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 (ENR)
- All Subjects Assigned (ASD)
- Safety Analysis Set (SAF)
- Full Analysis Set (FAS)
- Pharmacokinetic Full Analysis Set (PKFS)

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

- Screened
- Screen failure (defined as subjects who do not enter the trial and are not assigned treatment), reason for non-inclusion
- Assigned to treatment
- Assigned to treatment but not treated
- Treated
- Completed treatment

- Completed trial
- Discontinued from treatment, reason for premature discontinuation from treatment
- Discontinued from trial, reason for premature discontinuation from trial
- Discontinued from safety follow-up, reason for premature discontinuation from safety follow-up

Subjects enrolment will also be summarized by country and by age group (18-64, 65-84, >=85).

9.1. IMPORTANT PROTOCOL DEVIATIONS

Important protocol violations defined below will be listed for the ASD set:

- Trial drug not administered at all
- Severe violation of treatment compliance
    - Medical team will review subjects with treatment compliance outside 80% and 120% (refer to section 14.1) and decide if the violation is severe.
- Any deviation of inclusion/exclusion criteria should be considered as important violations.
- A severe violation to the restricted DMARD therapy (protocol table 4.2.2.1:1), as assessed by the medical team.

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 for ASD, FAS, SAF and PKFS:

- Age (years) at Inform Consent
- 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 subgroup at Informed Consent
  - AGE < 65 years
  - AGE >= 65 years
- Second age subgroup 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)
- Height at baseline (cm)
- Weight at baseline (kg)
- BMI at baseline (kg/m²)
- Country (please refer to section 7.2)
- Region (please refer to section 7.2)

The following baseline disease characteristics will be presented for FAS and SAF:

- Duration of rheumatoid arthritis (years) at Informed Consent.
- Individual parameters of ACR improvement criteria at baseline:

1. Swollen joint counts (66 joints) at baseline

2. Tender joint counts (68 joints) at baseline
3. Patient's assessment of pain at baseline
4. Patient's global assessment of disease activity at baseline
5. Physician's global assessment of disease activity at baseline
6. Patient's assessment of physical function, as measured by the HAQ-DI, at baseline
7. C-reactive protein (CRP) at baseline

- Erythrocyte sedimentation rate (ESR) at baseline
- Disease Activity Score 28-Erythrocyte sedimentation rate (DAS28-ESR) at baseline
- Disease Activity Score 28-Erythrocyte sedimentation rate (DAS28-CRP) at baseline

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

- Immunogenicity (proportion of subjects with positive ADAs result) at baseline
- Neutralizing anti-drug antibodies results at baseline
- Infection screen (for hepatitis B, hepatitis C, HIV test)
- Tuberculosis (TB) test
- Rheumatoid factor (RF) and anti-CCP antibodies

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

10.1. DERIVATIONS

- Age (years) = (date of consent– date of birth)/365.25
- BMI (kg/ m2) = weight (kg)/ height (m)2
- Duration of rheumatoid arthritis (years) = (date of informed consent - date of first diagnosis + 1)/ 365.25
- Joint counts:
  - Swollen joint counts (66 joints)
  - Tender joint counts (68 joints)

Refer to section 15.2.1.2 for further calculation details

- DAS28
  - DAS28 (CRP) = 0.56*√(TJC28) +0.28*√(SJC28)+0.014*GH+0.36*ln(CRP+1)+0.96
  - DAS28 (ESR) = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*ln(ESR) + 0.014*(GH)

  Where:

  TJC28 = 28 joint count for tenderness
  SJC28 = 28 joint count for swelling
  ln(CRP) = natural logarithm of CRP
  ln(ESR) = natural logarithm of ESR
  GH = the General Health component of the DAS, which is the patient's global assessment of disease activity.

ESR local value will be used for the DAS28 (ESR) calculation.

The following 28 joints will be evaluated for swelling and tenderness based on the eCRF entry

- 8 proximal interphalangeal (PIP) joints of the fingers (eCRF: right and left PIP2, PIP3, PIP4, PIP5)
- the interphalangeal (IP) joints of the thumbs (eCRF: right and left IP thumb)
- the 10 metacarpophalangeal (MCP) joints (eCRF: right and left MCP 1 – MCP 5)
- the wrists (eCRF: right and left wrist)
- elbows (eCRF: right and left elbow)
- shoulders (eCRF: right and left shoulder)
- knees (eCRF: right and left knee)

In determining the TJC28 and SJC28, if a joint evaluation is missing or 'Not done' at baseline (please refer to section 6.2 for baseline definition), it will not contribute to the joint counts at baseline and all subsequent visits (i.e., will be treated as 'Not Done'). If at least half but not all joints are evaluable (at least 14 joints for the 28 joint count with eCRF values 'present' or 'absent'), then the observed prorated tender/swollen joint count will be calculated. The prorated scores will be adjusted based upon the number of evaluable joints: the counted score will be multiplied by 28 and divided by the number of joints evaluated. For example, if only 25 of the 28 joints are assessed at a visit and 8 of those 25 are tender/swollen (eCRF value 'present'), the prorated joint count is 8/25×28 = 8.96. This value, 8.96 (not 8) will be used for DAS28 (ESR) score calculation. If less than half of the joints are evaluable (eCRF value 'not done' or missing), the number of tender/swollen joints is missing.

The General Health component of the DAS28(ESR) is Patient's global assessment of disease activity visual analysis scale (VAS) as collected in the eCRF and the ESR values provided by the local laboratory will be used for the

DAS28(ESR) calculation.

In the situation where the diagnosis date is partial or missing, the corresponding durations will be presented based on the imputations specified in APPENDIX 2.

11. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History information will be presented for the SAF. Medical History conditions are defined as those conditions which stop prior to or at Screening.

The system organ classes will be sorted by internationally agreed European Medicines Agency System Organ Class (EMA SOC) order (refer to APPENDIX 3), preferred terms (PT) will be sorted by decreasing frequencies (within system organ class).

Data captured on the "Medical and surgical history" page of the eCRF and on the "Concomitant Surgical Procedures" page of the eCRF will be merged together and assigned to prior, concomitant, or post-treatment phase.

Surgical and Medical History will be coded using MedDRA version 18.1 or higher.

See APPENDIX 2 for handling of partial dates for medical history, surgeries and procedures; if it is not possible to define an 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 (prior only).
- 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).

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

12. MEDICATIONS

Medications will be presented for the SAF and coded using WHO Drug Dictionary version SEP2015 or higher.

No ATC class coding will be performed.
The medical terms will be summarized by generic medication name.
The generic medication name will be sorted by decreasing frequencies.

See APPENDIX 2 for handling of partial dates for medications; if 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 or 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 all prior (respectively concomitant) prohibited/restricted medications outlined in CTP table 4.2.2.1:1, taken by at least one subject which may significantly impact efficacy assessment as determined by the trial medical advisor will be summarized in tables (overall for the FAS).

13. TRIAL MEDICATION EXPOSURE

Exposure to trial medication will be presented for the FAS and SAF.

The proportion of subjects treated at each planned visit (administration every two weeks from Day 1 to Day 337) will be presented.

Descriptive statistics for the number of injections from Day 1 up to Week 48 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: >= 1 day, >= 2 weeks, >= 4 weeks, >=12 weeks, >=24 weeks, , >=52 weeks.

13.1. DERIVATIONS

The date of first and last trial medication administration will be taken from the eCRF "Self-Administration of trial medication" page. Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

Duration of exposure (weeks) = (date of last injection - date of first injection + 1)/ 7.

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

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 for the FAS and SAF.

A first calculation will be based on the count of syringe boxes and/or labels in the eCRF. A second calculation will take into account the approximate left-over percentage of the pre-filled syringe volume in case the full volume was not injected.

Descriptive statistics for drug accountability compliance overall, overall until Week 12 and overall until Week 24 will be presented.

Descriptive statistics for pre-filled syringe volume compliance will be presented at each planned visit, overall, overall until Week 12 and overall until Week 24.

14.1. DERIVATIONS

Compliance will be calculated for subjects having attended the visit. A subject is considered having attended the visit if the indicated visit is captured in the eCRF database. Two types of compliances will be computed: drug accountability compliance and compliance (based on the left-over percentage of the pre-filled syringe volume).

Drug accountability compliance

Compliance with trial medication—based on the drug accountability data—will be calculated as the number of syringes injected (total dispensed – total unused + administered at site) divided by the prescribed number of syringes expressed as a percentage, see calculations below. The number of syringes will be captured in the two eCRF pages: Self-Administration of trial medication (if the administration was on site) and Trial medication Dispensation and collection (if the administration was at patient's home). The number of syringes required to be taken per week is 0.5.

- Overall Compliance by Week 12 and Overall Compliance by Week 24 will include unscheduled visit data and will be calculated by:

    1. Summing the number of syringes dispensed until 12 (resp. 24) Weeks exclusively and the number of syringes administered on site until 12 (resp. 24) Weeks inclusively, and subtracting the number of syringes unused until 12 (resp. 24) Weeks inclusively

    2. Multiplying by two the above quantity and dividing by the number of weeks between the first administration date and visit date Week 12 (resp. 24) plus 2 weeks

    3. Multiplying by 100 to express compliance as a percentage.

For subjects who permanently stop the trial medication prior to Week 12 (resp. 24), the "Date of Visit X(n)" will be replaced by the date of last administration of trial medication.

- Overall Compliance to trial medication will include unscheduled visit data and will be calculated by:

  1. Summing the number of syringes dispensed over the study, the number of syringes administered on site over the study, and subtracting the number of syringes unused over the study

  2. Multiplying by two the above quantity and dividing by the number of weeks between the first and last administration date plus 2 week

  3. Multiplying by 100 to express compliance as a percentage.

Compliance

Compliance with trial medication will be based on the "Self-Administration of trial medication" eCRF data.

The amount of drug to be administered is 0.8mL. The compliance will be based on the approximated left-over percentage of the pre-filled syringe volume in % (eCRF data) and the total volume (0.8mL considered as 100%) and calculated as amount of drug administered divided by the amount of drug to be administered expressed as a percentage, see calculations below. If the administration of trial medication occurred at home, one will assume 100% of the volume was administered if the administration occurred (i.e. "Was trial drug administered?" reported as "Yes").

- "Per Visit" Compliance to trial medication will be calculated at every administration timepoint as follows:

  Compliance (%) = 100 – Approximated left-over percentage of the pre-filled syringe volume as indicated in eCRF.

- Overall Compliance by Week 12 and Overall Compliance by Week 24 will be calculated as mean of the "per visit" compliance until Week 12 (resp. Week 24).

- Overall Compliance to trial medication will be calculated as mean of the "per visit" compliance.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

No primary efficacy endpoint.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the FAS and are summarized below:

Secondary endpoints	Population, imputation method	Analysis
Change from Baseline of DAS28(ESR) at Week 48	FAS, LOCF	Descriptive
Proportion of subjects meeting the ACR20 response criteria at Week 48	FAS, NRI/LOCF	Descriptive
Proportion of subjects who meet the ACR/EULAR definition of remission at Week 48	FAS, no imputation method	Descriptive
Proportion of subjects with EULAR response at Week 48	FAS, no imputation method	Descriptive

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. DAS28 endpoint

A secondary endpoint is:

- The change from Baseline in trial 1297.2 in DAS28 (ESR) at Week 48 of trial 1297.3

DAS28 (ESR) score will be derived at every planned efficacy assessment visit using the formula described in section 10.1. The change from Baseline in DAS28 (ESR) (baseline-post baseline) will be calculated for every planned post-baseline efficacy assessment visit.

15.2.1.2. ACR20 endpoint

A secondary efficacy endpoint is

- The proportion of subjects meeting the ACR20 response criteria (based on improvement since Baseline in trial 1297.2) at Week 48 of trial 1297.3.

ACR20 response will be calculated at every planned efficacy assessment visit.

A subject has an ACR20 response if all of the following occur:

- A ≥ 20% improvement in the swollen joint count (66 joints)
- A ≥ 20% improvement in the tender joint count (68 joints)
- A ≥ 20% improvement in at least three of the following assessments:
  - Patient's assessment of pain
  - Patient's global assessment of disease activity
  - Physician's global assessment of disease activity (see below for more details).
  - Patient's assessment of physical function, as measured by the Health Assessment

Questionnaire – Disability Index (HAQ-DI)

- Acute phase reactant (CRP).

Improvement is assessed as the decrease in a component relative to baseline, (100×(baseline - post baseline)/baseline).

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

If a joint evaluation is missing or 'Not done' at baseline (please refer to section 6.2 for baseline definition), it will not contribute to the joint counts at baseline and all subsequent visits (i.e., will be treated as 'Not Done'). If at least half but not all joints are evaluable (at least 33 joints for the 66 joint count for swelling with eCRF values 'present' or 'absent', at least 34 joints for the 68 joint count for tenderness with eCRF values 'present' or 'absent'), then the observed prorated tender/swollen joint count will be calculated.

The prorated scores will be evaluated based upon the number of evaluable joints: the counted score will be multiplied by 66 for swelling or 68 for tender joint count and divided by the number of joints evaluated. For example, for tender joint count, if only 45 of the **68** joints are assessed at a visit and 18 of those 45 are tender (eCRF value 'present'), the prorated tender joint count is 18/45×68 = 27.2. This exact value, 27.2 (and not 18) will be used for ACR20 score calculation. For swollen joint count, if only 45 of the **66** joints are assessed at a visit and 18 of those 45 are swelling (eCRF value 'present'), the prorated swollen joint count is 18/45×66 = 26.4. This exact value, 26.4 (and not 18) will be used for ACR20 score calculation.

If less than half of the joints are evaluable (eCRF value 'not done' or missing), the number of tender/swollen joints is missing.

The central laboratory data for CRP and eCRF data for all other ACR20 components will be used for the calculation.

Patient's assessment of pain as well as patient's and physician's global assessment of disease activity accessed using the VAS of 100 mm.

Patient's assessment of physical function will be assessed using HAQ-DI. The calculation of this index is described below. The HAQ-DI is composed of 20 items. There are eight categories, each of which has at least two component questions:

1. Dressing and grooming
2. Arising
3. Eating
4. Walking
5. Hygiene
6. Reach
7. Grip
8. Common daily activities.

For each of the categories, subjects report the amount of difficulty they have in performing two or three specific sub-category items, or also known as components, or component variables.

0 = without ANY difficulty

1 = with SOME difficulty

2 = with MUCH difficulty

3 = UNABLE to do.

If a component question is left blank, then the score for that category is determined by the remaining completed question(s).

The subject must have a score for at least 6 of the 8 categories. If there are less than 6 categories completed, a HAQ-DI cannot be computed, whether the missing categories are due to missing values or they do not apply to the respondent.

Calculation of HAQ-DI score:

1. Sum the eight category scores*

*A category score is determined from the highest score of the sub-categories, or components, in that category, except when aids or devices are taken into account (see below). For example, if there are three sub-category items (as in the category ARISING), and the subject responds with a 1, 2, and 0, respectively, to the three sub-category items, the score for the ARISING category will be a 2.

2. Divide the sum by the number of categories answered (range - 6-8)

Scoring AIDS OR DEVICES or help companion variables:

1. When there are NO aids or devices, or help indicated for a category, the category's score is not modified.

2. When aids or devices or help ARE indicated by the subject, the score for the category item is raised from a 0 or a 1 to a 2, but if the subject's highest score for that sub-category is a 2, it stays a 2 (the same for 3)

15.2.1.3. ACR/EULAR remission

A secondary efficacy endpoint is

- The proportion of subjects who meet the ACR/EULAR definition of remission (based on improvement since Baseline in trial 1297.2) at Week 48 of trial 1297.3.

To have the ACR/EULAR Remission, the subject must satisfy all of the following criteria:

- Tender joint count (TJC) (68) ≤ 1
- Swollen joint count (SJC) (66) ≤ 1
- CRP ≤ 1mg/dL
- Patient global assessment ≤ 10 (on a 0-100 scale)

15.2.1.4. EULAR response

A secondary efficacy endpoint is

- The proportion of subjects with EULAR response (good response, moderate response or no response) (based on DAS28 (ESR) improvement since Baseline in trial 1297.2) at Week 48 of trial 1297.3.

Improvement in DAS28 (ESR) will also be categorized using the EULAR response criteria:

	DAS28 Improvement		
DAS at endpoint	≥1.2	>0.6 and <1.2	≤0.6
≤3.2	Good Response	Moderate response	No Response
>3.2 and ≤5.1	Moderate response	Moderate response	No Response
>5.1	Moderate response	No Response	No Response

Where DAS28(ESR) improvement is computed as:
- DAS28(ESR) at 1297.2 baseline – DAS28(ESR) at Week X.

15.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLES

15.2.2.1. Missing data method for DAS28

Last observation carried forward (LOCF) will be used for imputation of missing component variables prior to DAS28 (ESR) score calculation.

15.2.2.2. Missing data method for ACR20

Missing ACR20 data will be imputed at Week 48 using a combination of non-responder imputation and LOCF methods.

Table 1 details exactly where the LOCF / NRI imputation will be applied.

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

	…prior to week X	
Analysis (FAS)	Discontinued treatment[#]	Did NOT discontinue treatment
ACR20 computable using observed data at week X	No (NRI applied)	Yes/No (observed)
ACR20 NOT computable using observed data at week X	No (NRI applied)	Yes/No (LOCF applied)$

[#] lost to follow-up from trial 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 ACR20 component data will be imputed using the last observation carried forward (LOCF) method

and ACR20 will be calculated based on the imputed component data.

Last observation will be carried forward as many time as needed.

Step 2: The imputed ACR20 will be set to non-responder at Week 48, if the subject

- discontinue treatment prior to Week 48
- are lost-to-follow-up prior to Week 48
- have any severe violation related to any therapy that may significantly impact efficacy assessment prior to Week 48

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 SEPR2015 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

15.2.2.3. Missing data method for ACR/EULAR remission and EULAR response

Efficacy data for ACR/EULAR remission and EULAR response will not be imputed.

15.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

Secondary efficacy endpoints will be presented for FAS.

Descriptive statistics will be provided for each secondary endpoint.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

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

The primary endpoint is defined as:

- The number (proportion) of patients with drug-related AEs during the treatment phase (with onset date between start of treatment and 10 weeks after the last dose of trial medication, i.e. treatment-emergent AE, refer to Section 16.1.1.1).

Other safety endpoints will be:

- The 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)
- The proportion of patients who experience hypersensitivity reactions
- The proportion of patients who experience DILI
- The proportion of patients with injection-site reactions
- The proportion of patients with antidrug antibodies (ADAs) at Week 12, Week 24, and Week 48
- The proportion of patients with neutralizing antidrug antibodies (nABs) at Week 12, Week 24, and Week 48
- The proportion of patients who discontinue due to a drug-related AE

Other safety evaluations will include: physical examination, vital signs (blood pressure, pulse rate, respiratory rate, body temperature), 12-lead ECGs, laboratory tests, and continuous AE monitoring.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using the MedDRA central coding dictionary, Version 18.1 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).

An overall summary of the number of subjects, percentages, number of events and patient-year incidence rate 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.

All the outputs described in this section will be presented according to the initial randomization and re-randomization of trial 1297.2 unless specified otherwise.

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 in severity on or after the first dose of 1297.3 trial medication and prior to the last date of 1297.3 trial medication + 10 weeks inclusive.

Non-TEAEs will be classified as "Prior treatment" 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.

16.1.1.2. Patient-Year incidence rate

Patient-year incidence rate per 1000 years for AEs will be calculated as follows:

(Number of subjects with at least one AE) / (Patient-Year) * 1000

where Patient-Year is the sum of time at risk for each subject (days) in the treatment group divided by 365.25.

The time at risk (years) per subject is derived as following:

- subject had at least one AE with specific criterion:

time at risk (days) = start date of first AE meeting the specific criterion – start of treatment +1

- subject without AE with specific criterion:

time at risk (days) = end of treatment + 70 – start of treatment +1

Patient-year incidence rate per 1000 years for TEAEs, SAEs, related TEAEs, TEAEs leading to discontinuation of trial medication, TEAEs leading to Death and AEs of special interest (AESI) will be calculated using the above algorithm.

16.1.2. ALL TEAES

Number of subjects, percentages, number of events and patient-year incidence rate of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity, relationship to trial medication and subgroups (refer to section 7.5.1).

A summary of 1297.2 trial TEAEs occurring during the 1297.3 screening phase will be prepared.

16.1.2.1. Intensity

Intensity is classified 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

An investigator-assessed drug-related AE is defined as an AE with a relationship to trial medication ticked “yes” 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 AE more than once within that SOC/PT, and at least 1 episode is related, the AE will be considered related for 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.

For TEAEs leading to permanent discontinuation of trial medication, number of subjects, percentages, number of events and patient-year incidence rate by SOC and PT will be prepared.

The AEs causing treatment modification or Drug Withdrawn will be listed.

16.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as ”Serious” on the AEs page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.

Number of subjects, percentages, number of events and patient-year incidence rate of Serious TEAEs by SOC and PT will be prepared.

Number of subjects, percentages, number of events and patient-year incidence rate of Non-Serious TEAEs with incidence in preferred terms strictly greater than 5% in at least one of treatment groups by SOC and PT will be prepared.

The SAEs and Non-SAEs will be listed.

16.1.5. Related Serious Adverse Events

Number of subjects, percentages, number of events and patient-year incidence rate of Related Serious TEAEs by SOC and PT will be prepared.

16.1.6. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as ”Results in death” or with outcome ”Fatal” on the AEs page of the eCRF. Number of subjects, percentages, number of events and patient-year incidence rate of TEAEs leading to death by SOC and PT will be prepared.

All AEs leading to death will be listed.

16.1.7. ADVERSE EVENTS OF SPECIAL INTEREST

An overall summary of the number of subjects, percentages, number of events and patient-year incidence rate within each of the categories described in the sub-section below will be provided by SOC and PT.

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 AEs page of the eCRF.

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 AEs page of the eCRF.
- AEs which are both infections and identified by medical advisor as requiring class IV (intravenous) antibiotics.

Serious infections events of special interest are those events both identified as serious infections adverse events and recorded as “Adverse Event of Special Interest” equal to “Yes” on the Adverse Events page of the eCRF.

Treatment Emergent Infections / Serious Infections will be tabulated separately.

Infections / Serious Infections will be listed.

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

Treatment Emergent Hypersensitivity reactions will be tabulated separately.

Hypersensitivity reactions will be listed.

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 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.

Treatment Emergent DILI will be tabulated separately.

Drug Induced Liver Injury (DILI) will be listed.

16.1.7.5. Injection-site reactions

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

- Administration site reactions NEC
- Application and instillation site reactions
- Injection site reactions
- Infusion site reactions

The number and percentage of subjects with injection site reactions will be summarized by treatment for each injection site reaction (swelling, induration, heat, redness, pain, itching, bruising, other).

Treatment Emergent Injection-site reactions as well as injections site reactions types will be tabulated separately.

Treatment Emergent Injection-site reactions as well as injections site reactions types 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 reactions adverse events of special interest 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.

Treatment Emergent Anaphylactic reactions will be tabulated separately.

Anaphylactic reactions will be listed.

16.1.8. AEs OCCURRING 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, number of events and patient-year incidence rate of AEs 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.

16.1.9. NON-SERIOUS ADVERSE EVENTS LEADING TO DISCONTINUATION OF TREATMENT

Non-serious adverse events leading to discontinuation of treatment (recorded as "Is this a serious adverse event?" equal to "No" and "Action taken with trial drug due to AE?" equal to "Drug Withdrawn" on the Adverse Events page of the eCRF).

Number of subjects, percentages, number of events and patient-year incidence rate of treatment emergent non-serious adverse events leading to discontinuation of treatment by SOC and PT tables will be prepared.

Non-serious adverse events leading to discontinuation of treatment will be listed.

16.1.10. FURTHER SELECTED ADVERSE EVENTS

Further selected adverse events were not defined in the CTP and were identified to support a project-level integrated safety summary of additional important safety topics of the class.

16.1.10.1. Hepatitis B Virus (HBV) reactivation

Hepatitis B Virus (HBV) reactivation are those events recorded as MedDRA LLT search "reactivation of hepatitis B".

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Hepatitis B Virus (HBV) reactivation by SOC and PT tables will be prepared.

Hepatitis B Virus (HBV) reactivation will be listed.

16.1.10.2. Haematological disorders

Haematological disorders are those events recorded as:

- BIcMQ "Haematologic disorders" (narrow and broad)(refer to APPENDIX 5)

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Haematological disorders by SOC and PT tables will be prepared

Haematological disorders will be listed.

16.1.10.3. Neurological events (Demyelinating disorders)

Neurological events (Demyelinating disorders) are those events recorded as:

- SMQ "Demyelination" (narrow)

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Neurological events (Demyelinating disorders) by SOC and PT tables will be prepared.

Neurological events (Demyelinating disorders) will be listed.

16.1.10.4. Systemic lupus erythematosus

Systemic lupus erythematosus are those events recorded as:

- SMQ "Systemic lupus erythematosus" (narrow)

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Systemic lupus erythematosus by SOC and PT tables will be prepared.

Systemic lupus erythematosus will be listed.

16.1.10.5. Sarcoidosis

Sarcoidosis are those events recorded as:

- BIcMQ "Sarcoidosis" (narrow)

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Sarcoidosis by SOC and PT tables will be prepared.

Sarcoidosis will be listed.

16.1.10.6. Stevens-Johnson syndrome

Stevens-Johnson syndrome are those events recorded as:

- PT "Stevens-Johnson syndrome"

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Stevens-Johnson syndrome by SOC and PT tables will be prepared.

Stevens-Johnson syndrome will be listed.

16.1.10.7. Erythema multiforme

Erythema multiforme are those events recorded as:

- PT "Erythema multiforme"

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Erythema multiforme by SOC and PT tables will be prepared.

Erythema multiforme will be listed.

16.1.10.8. Autoimmune hepatitis

Autoimmune hepatitis are those events recorded as:

- SMQ "Hepatitis, noninfectious" (narrow)

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Autoimmune hepatitis by SOC and PT tables will be prepared.

Autoimmune hepatitis will be listed.

16.1.10.9. Malignancies

Malignancies are those events recorded in BIcMQ "Malignancies" (narrow and broad) (refer to APPENDIX 5).

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Malignancies by SOC and PT tables will be prepared.

Malignancies will be listed.

16.1.10.10. Chronic heart failure

Chronic heart failure are those events recorded in SMQ "Cardiac failure" (narrow).

Number of subjects, percentages, number of events and patient-year incidence rate of Treatment Emergent Chronic heart failure by SOC and PT tables will be prepared.

Chronic heart failure will be listed.

16.2. DEATHS

If any patients die during the trial as recorded on the completion or safety follow-up page of eCRF, the information will be summarized and listed.

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 4.

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 a period of 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 in trial 1297.2 by visit (for quantitative measurements)

- Shifts in Rheumatology Common Toxicity Criteria (RCTC) grading, from baseline in trial 1297.2 by visit (for gradable parameters, see APPENDIX 4)

- Shifts from baseline category (Low/ Normal/ High) in trial 1297.2 by visit (for non-gradable parameters except urinalysis parameters and ADA)

- Shift from baseline category (Negative/ Positive) in trial 1297.2 by visit (for urinalysis non-gradable parameters)

- Box plots for ESR, CRP, hemoglobin, leukocytes (equivalent to white blood cells), platelets, AST, ALT, bilirubin, creatinine, cholesterol

- Plots for time course of gradable safety parameters for subjects having at least one value with toxicity grade 3 or 4 (RCTC grading is described section 16.3.3)

- Proportion and frequency of possible Hy's law subjects

- Proportion and frequency of possible Drug Induced Liver Injuries

- 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:

    1. 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

    2. 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:

1. Category 1: ALT or AST >=3xULN and TBL >=2xULN within the same sample

2. 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 :

1. Category 1 : AST and/or ALT ≥3 times ULN and TBL ≥2 times ULN within the same sample

2. Category 2: 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 MARKEDLY ABNORMAL CRITERIA

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

- Low: Below the lower limit of the laboratory reference range.

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

- High: Above the upper limit of the laboratory reference range.

16.3.3. RCTC GRADING FOR LABORATORY DATA

Laboratory results will be classified according to the Rheumatology Common Toxicity Criteria v.2.0.

Only programmable parts of definitions will be performed.

The "Grade 0" will be introduced to indicate that a certain laboratory value can be seen as "normal" and does not fulfill the criteria of RCTC grading. For uncertain cases (for example when the values can be assigned to grade 0 based on the normal range and grade 1 or 2 based on the toxicity criteria), a medical check will be performed, to determine the correct grade.

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 clinical significant" and "abnormal, clinical 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)
- Sitting Respiratory Rate (breaths/min)
- Temperature (°C)

The 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

Proportion 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.

Physical examination data will be listed.

16.7. OTHER SAFETY ASSESSMENTS

16.7.1. IMMUNOGENICITY

The following summaries will be provided for ADAs and nABs samples by visit (Week 12, Week 24 and Week 48) and overall:

- Number and proportion of subjects with ADA/nAB sampling results by visit:
  - Negative
  - Positive
  - Total reportable (= sum of Negative and Positive)o
  - Not Reportable (=samples which should have been taken per protocol but no result is available (due to many reasons). Samples from patient that discontinued (drop-outs) or patients that have not reached a defined time-point yet, are not considered non-reportable but reduce the number of total samples available.)
  - Total (= sum of Total Reportable and Not Reportable)
- Descriptive statistics of ADA titer will be provided by visit when available.

The ADA and nABs results will be listed as well.

The following summaries figures will be provided for Immunogenicity data:

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

16.7.2. PREGNANCY TEST

Pregnancy, described as a patient with at least one pregnancy result Plus, will be summarized.

Descriptive table will be presented by treatment group according to the initial and re-randomization in trial 1297.2 on SAF.

The pregnancy results will be listed as well.

16.7.3. TUBERCULOSIS TEST

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

The TB test results will be listed as well.

17. PHARMACOKINETIC DATA

17.1. PHARMACOKINETIC ENDPOINTS

The PK analysis will be based on a population based approach, which is not a part of this SAP.

This SAP contains the description of the planned presentation of the measured plasma concentrations.

17.2. GENERAL CONSIDERATION

Missing data will not be replaced.

For data presentation the following conventions will apply:

Sampling visits performed outside the allowed time window will be reported and flagged in the table. The flagged sampling results will be excluded from the descriptive statistics and from the figures (with exception of the scatter plot of individual plasma concentrations per treatment group over time).

Descriptive statistics of concentrations at specific visits will be calculated only when at least 2/3 of the individuals have concentrations measurements within the validated concentration range of the assay (that means between lower and upper limit of quantification as reported in the BA transfer). The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples actually drawn.

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

17.3. PLASMA CONCENTRATIONS PRESENTATION

The PK concentration data will be based on PKFS set.

Descriptive statistics will contain at least N, geometric mean (gMean), geometric coefficient of variation (gCV, given in %), arithmetic mean, SD, coefficient of variation (CV, given in %), minimum, median, and maximum of a parameter.

CV: The coefficient of variation (CV) will be calculated by the formula:

CV = (SD/mean)x100

gMean, gCV: The geometric mean (gMean) and geometric coefficient of variation (gCV, given in %), will be calculated by the formulae:

$$\text{gMean} = \exp\left[\frac{1}{n}\sum_{i=1}^{n}\ln(x_i)\right] = \exp\left[\overline{\ln(x_i)}\right]$$

$$\text{gCV}(\%) = 100 \cdot \sqrt{\exp\left[\text{Var}(\ln(x_i))\right] - 1}$$

where

$$\text{Var}(\ln(x_i)) = \frac{1}{n-1}\sum_{i=1}^{n}\left[\ln(x_i) - \overline{\ln(x_i)}\right]^2$$

The following summaries will be provided for plasma concentration data:

- All measured plasma concentrations will be listed by 1297.2 treatment sequence and overall and planned time point and descriptive statistics per time point.
- A spaghetti plot of individual and gMean plasma concentrations over time by 1297.2 treatment sequence and overall (gMeans shown per planned time points connected by a line)
- A scatter plot of individual plasma concentrations after the preceding dose over time by 1297.2 treatment sequence and overall.

18. REFERENCES

Ware JE Jr., Kosinski M, Bjorner JB, et al. 2008. SF-36v2® Health Survey: Administration guide for clinical trial investigators. Lincoln, RI: QualityMetric Incorporated.

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 super-scripts, 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 (eg Vital Signs) followed by metric (eg 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

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.
  Eg (<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 – eg "*", "$", "#", "@", "&" 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 first footnote, 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

Treatment Groups will depend on treatment assignment in Trial 1297.2 (randomization/re-randomization) and will

be named as follows:

- BI 695501 to BI 695501
- US-licensed Humira® to US-licensed Humira®
- US-licensed Humira® to BI 695501

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

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

PRESENTATION OF VISITS

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

Long Name (default)	Short Name
Day -14	D-14
Day 1	D1
Day 43	D43
…	…
Day 337	D337

In addition, the corresponding weeks will be added for each pre-specified visit in protocol flow chart to long name (Day 43, 85, 127, 169, 225, 281, 337). E.g.: Day 43 (Week 6).

LISTINGS

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

- treatment group
- center-subject ID
- date including Study day (where applicable)

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR DISEASE DURATION

DATE	ACTION
Partial	Impute date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown)

ALGORITHM FOR BIRTH DATE

DATE	ACTION
Partial	Impute date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown)

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

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
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

START DATE	STOP DATE	ACTION
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 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

START DATE	STOP DATE	ACTION
		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

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

START DATE	STOP DATE	ACTION
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

APPENDIX 4. LABORATORY ASSESSMENTS

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

APPENDIX 5. **BIcMQs**


BIcMQ_19.0_Administration_site_reactio


BIcMQ_19.0_Haematologic disorders


BIcMQ_19.0_Sarcoidosis