16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan V1.0, dated 09 Jan 2017

Bioanalytical Report –	Determination of BI 695501 Plasma Samples of Clinical Trial Protocol Number 1297.13
Bioanalytical Report –	Detection of Total Anti-Drug Antibodies and Neutralizing Antibodies Against BI 695501 in Plasma Samples of Clinical Trial Protocol Number 1297.13

STATISTICAL ANALYSIS PLAN

1297.13

Randomized, single-dose, parallel-arm, open-label Phase I trial to compare the pharmacokinetics, safety and tolerability of BI 695501 administered subcutaneously via prefilled syringe or autoinjector

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V1.0, 09JAN2017

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 09JAN2017) for Protocol 1297.13.

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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 09JAN2017) for Protocol 1297.13.

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	09JAN2017	[redacted]	Not Applicable – First Version

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[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Autoinjector
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BI	Boehringer-Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
CI	Confidence Interval
DBL	Database Lock
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ENR	Enrolled Set
EOI	End of Infusion
EOT	End of Treatment
FAS	Full Analysis Set
IGRA	Interferon-Gamma Release Assay
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing Anti-Drug Antibody
NOA	Not analyzed
NOS	No available sample

NOR	No valid result
PFS	Prefilled syringe
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PPAS	Per Protocol Analysis Set
PT	Preferred Term
RND	Randomized Set
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SFU	Safety Follow-up
SI	Système International
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SOP	Standard Operating Procedure
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TLF	Tables Listings Figures
ULN	Upper Limit of Normal
ULQ	Above the upper limit of quantification
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of pharmacokinetics (PK), tolerability, safety and immunogenicity data for Protocol 1297.13. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. The derivation and analyses description related to PK, except the statistical model, are provided by the sponsor PK specialist. The description of the safety analyses and statistical model for PK parameter are provided by [redacted]

This statistical analysis plan (SAP) is based on protocol version 1.0, dated 23 August 2016.

2. TRIAL OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this trial is to compare the PK of 40 mg of BI 695501 administered using an autoinjector and 40 mg of BI 695501 administered using a prefilled syringe following a single subcutaneous (s.c.) injection in the thigh. In particular: C_{max}, AUC_{0-1368} and $AUC_{0-\infty}$.

2.2. SECONDARY OBJECTIVES

The secondary objective is to assess safety.

[redacted]

3. TRIAL DESIGN

3.1. GENERAL DESCRIPTION

Trial 1297.13 is a 14-week, randomized, single-dose, open-label trial in healthy volunteers.

Each subject will receive one subcutaneous injection with either 40 mg BI 695501 autoinjector (AI) or 40 mg BI 695501 prefilled syringe (PFS) followed by an observation period of approximately 57 days and an additional safety follow-up period up to 70 days after the trial drug administration. Subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomly assigned to one of the two groups with a 1:1 allocation ratio. Randomization will be stratified by site (2 levels and for logistical reasons only) and body weight category (low: ≤ 60.0 kg, medium: > 60.0 to < 90.0 kg, high: ≥ 90.0 kg).

It is planned to include 160 healthy male and female subjects (at least 30% of each gender will be included in the trial) with a broad range of weight for the primary analysis report describing the PK profiles of BI 695501 given in a PFS and an AI as well as the assessments of safety and immunogenicity. All efforts will be made to enroll subjects in all subgroups, in order to ensure a wide distribution of weight in the study.

This trial will have a screening period of up to 28 days. The subject will check in to the trial center on Day-1, will be randomized and dosed on Day 1, and will be resident until the Day 8 discharge procedures are complete. All subjects will remain in the clinic until Day 8 after dosing. The subject will then return to the clinic for 7 ambulatory visits on Days 10, 15, 22, 29, 36, 43 and 57 (End-of-Trial [EOT] visit).

Additionally, all adverse events (AEs), regardless of relatedness, will be collected until up to 10 weeks after the administration of trial medication. Adverse events not fully resolved at the safety follow-up (SFU) visit (Day 70 visit) will be followed until recovery or in case of persistency, sufficient characterization has been achieved and the investigator and medical monitor agree to not pursue them further.

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

Per the protocol, hepatic injuries, anaphylactic reactions, serious infections and hypersensitivity reactions are defined as Adverse Events of Special Interest (AESIs). In addition, all treatment-emergent infections will be analyzed, for consistency with the analysis performed on 1297.6 trial.

No PK sensitivity analysis is planned per the protocol. However, if PK profiles suggest biologically implausible results for s.c. administration or suggest extreme values (high or low), then a sensitivity analysis may be conducted post-hoc to repeat the analyses described in section 16.1 without the patients with implausible or extreme results. The decision of a sensitivity analysis addition will be taken

by Boehringer-Ingelheim (BI).

Per the protocol, one of the primary PK endpoint is the $AUC0_{0-\infty}$ based on observed concentration at time of last measurable concentration. In addition, the $AUC0_{0-\infty}$ based on predicted concentration at time of last measurable concentration will be analyzed as a further PK endpoint.

4. .PLANNED ANALYSES

According to protocol section 7.4, no formal interim analysis will be performed for this trial.

The following analyses will be performed for this trial:

- Final Analysis

The planned analysis identified in this SAP will be performed by [redacted] Biostatistics (excluding PK descriptive analyses) and by BI (responsible for PK descriptive analyses and PK Tables, Listings, and Figures (TLFs) related to descriptive analysis) following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, and Sponsor Authorization of Analysis.

4.1. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by [redacted] Biostatistics (excluding PK descriptive analyses) and by BI (responsible for PK descriptive analyses and PK Tables, Listings, and Figures (TLFs) related to descriptive analysis) following Sponsor Authorization of this Statistical Analysis Plan, Database Lock (DBL), and Sponsor Authorization of Analysis Sets.

5. ANALYSIS SETS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted by BI during the report planning meeting 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 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]

No FAS is defined in this trial.

5.4. PER PROTOCOL ANALYSIS SET [PPAS]

No PPAS is defined in this trial.

5.5. SAFETY ANALYSIS SET [SAF]

The Safety Analysis Set (SAF) will contain all subjects in the ENR set who receive at least one dose of trial medication and subjects will be classified according to treatment received.

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

5.6. PHARMACOKINETIC ANALYSIS SET [PKS]

The Pharmacokinetic Set (PKS) will consist of all randomized subjects who receive the single dose of trial medication (BI°695501 using AI or BI°695501 using PFS), and have at least one evaluable primary PK parameter, and are without important protocol deviations or violations thought to have a relevant impact on the PK of BI 695501.

Pharmacokinetic parameters for a subject will be included in the analysis unless the subject has an important protocol violation relevant for the evaluation. Whether a protocol violation is relevant will be decided no later than in the report planning meeting.

Reasons for exclusion of single pharmacokinetic parameters may include (but are not limited to):

- Relevant time deviations
- Use of restricted medications
- Dosing errors
- Missing samples relevant for correct estimation of PK parameters C_{max} or AUC

It will also be decided in the report planning meeting which subjects are to be excluded from the PKS.

Important protocol violations will be defined before the final database lock.

In case of PK profiles suggesting biologically implausible results for s.c. administration or suggesting extreme values (high or low), then the patients with implausible or extreme results may be excluded from the PKS for a sensitivity analysis.

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 and single injection of trial medication, (Day 1 is the day of the first dose of trial medication) or, for subjects randomized but not treated, it is the day of randomization (Day 1).

Reference start date 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, Study Day, and any corresponding durations, will appear partial or missing in the listings.

6.2. BASELINE

Baseline is defined as the last non-missing measurement taken prior to drug administration (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered 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.

Unscheduled measurements (unless assigned to a planned visit number, as stated above) will not be included in by-visit summaries.

Early treatment termination data will not be included in by-visit table summaries and by-visit graphs.

Listings will include scheduled, unscheduled, retest and early discontinuation data collected in the electronic Case Report Form (e-CRF) database.

6.4. WINDOWING CONVENTIONS

The acceptable deviations from the scheduled time for PK assessments are:

- ±15 minutes for Day 1;

- ±2 hours from Day 2 to Day 10;

- ±1 day from Day 15 to Day 57.

The relevance of measurements outside the permitted time windows for their inclusion in the PK analysis will be assessed no later than at the Report Planning Meeting.

6.5. STATISTICAL TESTS

The default significance level will be 10%; confidence intervals will be 90% 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

Logarithmic transformation of PK parameters will be performed as follows:

- Ln (PK parameter) = natural logarithm of the PK parameter

6.7. SOFTWARE VERSION

Analyses provided by [redacted] will be conducted using SAS version 9.4 or higher. Analysis provided by BI will be using Phoenix WinNonlin Version 6.3 or higher and/or 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 analyses. For details of their inclusion in the models, see the specific analysis section.

- Treatment group (BI 695501 using AI or BI 695501 using PFS)
- Baseline body weight (continuous variable)

7.2. MISSING DATA

Missing PK data will be handled as described in section 16 of this analysis plan.

Missing safety data will not be imputed unless otherwise specified in section 15.

7.3. MULTIPLE COMPARISONS/ MULTIPLICITY

The relative bioavailability will be evaluated in an exploratory manner. No formal alpha adjustment is required.

7.4. EXAMINATION OF SUBGROUPS

7.4.1. RANDOMIZATION STRATIFICATION FACTORS

Disposition will be displayed for each randomization strata:

- Baseline body weight (≤60.0 kg, >60.0 - <90.0 kg, ≥90.0 kg),
- Site

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs provided by [redacted]

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 [redacted] Biostatistics.

9. DISPOSITION AND WITHDRAWALS

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

The counts of the following analysis sets will be presented:

- All Subject Randomized Set (RND)
- Safety Analysis Set (SAF)
- Pharmacokinetic Analysis Set (PKS)

The following subject disposition and withdrawals will be presented for the ENR set overall and by body weight group:

- Screened
- Screen failure (defined as withdrawn from trial prior to randomization)
- Randomized

- Randomized but not treated
- Completed treatment (assessed at Day 1)
- Completed trial (observational period, assessed at Day 57)
- Discontinued from trial, reason for premature discontinuation from trial
- Completed safety follow-up
- Discontinued from safety follow-up, reason for premature discontinuation from safety follow-up

Protocol violations relevant for primary PK analysis (as defined in section 5.6) will be presented for the RND set.

In addition, subject disposition by country and by age groups will be reported overall and will be displayed for ENR population for disclosure purpose.

The following age groups will be reported:

- 18 - 64 years
- 65 - 84 years

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the RND, SAF and PKS.

In this trial, there is a high probability that RND is equivalent to SAF. In order to avoid duplicate tables regarding demographic characteristics, it will be checked before the final DBL whether:

- Subjects were treated but not randomized
- Subjects were randomized but not treated
- Subjects did not receive the allocated treatment

If RND is equivalent to SAF, tables will be displayed for RND only. Otherwise, both populations will be considered.

In the same manner, tables will be repeated for PKS only if PKS is not equivalent to RND.

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

The following demographic and other baseline characteristics will be reported for this trial:

- Age (years)

- Age groups 1:
  - <65 years
  - ≥65 - <75 years
  - ≥75 years
- Age groups 2:
  - <65 years
  - ≥65 years
- 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)
- Weight (kg)
- Weight groups (equivalent to the stratification factor):
  - ≤60.0 kg,
  - >60.0 - <90.0 kg,
  - ≥90.0 kg.
- Height (cm)
- Body mass index (BMI) (kg/m^2)
- Smoking status (never smoked / is an ex smoker / currently smokes)
- Alcohol consumption (does not drink any alcohol / drinks alcohol but should not interfere with participation in trial / drinks alcohol and could interfere with participation in trial)

Any discrepancies between randomized strata and derived body weight group based on eCRF data will be reported in a subject level footnote.

10.1. DERIVATIONS

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

11. SURGICAL AND MEDICAL HISTORY

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

Surgical and Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or higher.

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

Only prior surgical and medical history will be presented by SOC (System Organ Class) and PT (Preferred Terms). They will be sorted by decreasing frequencies. All reported surgical and medical history will be listed.

12. MEDICATIONS

Medications will be presented for the SAF and coded using World Health Organization Drug Dictionary version (WHO DD) SEP2016 or higher.

No Anatomical Therapeutic Chemical (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, in the case where it is not possible to define a medication as prior or concomitant, 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 were ongoing at the time of administration or started during the trial (until end of trial date on Day 70).

All prior and concomitant prohibited/restricted medications outlined in protocol section 4.2.2.1 as determined by the trial medical advisor will be listed.

13. TRIAL MEDICATION EXPOSURE

The number of subjects receiving trial medication will be reported for the SAF.

Information about injection difficulty will be displayed according to the answers on page "Administration of Trial Medication" of the eCRF.

A listing will be created with the randomisation number, medication kit number, as well as injection site selected.

14. EFFICACY OUTCOMES

No efficacy outcomes will be analyzed in this trial.

15. 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 secondary safety endpoint is defined as the number (proportion) of subjects with drug-related treatment emergent adverse events (TEAEs) occurring from Day 1 through Day 70.

Safety and tolerability of the investigational products will be assessed based on:

- TEAEs (including clinically relevant findings from the physical examination and AESIs)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (Blood pressure, pulse rate, temperature)

- Local tolerability

15.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 19.1 or higher. SOCs will be sorted by internationally agreed European Medicines Agency (EMA) SOC order (refer to APPENDIX 4), PTs will be sorted by decreasing frequencies (within system organ class).

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

TEAEs are defined as AEs that started or worsened in severity on or after the first and single dose of trial medication up to 10 weeks (70 days) post dose.

See APPENDIX 2 for handling of partial dates for AEs. In case 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.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

15.1.1. ALL TEAES

Incidence of TEAEs will be presented by SOC and PT within each SOC and also broken down further by maximum severity and relationship to trial medication.

15.1.1.1. Intensity

Intensity is classed as mild/ moderate/ severe (increasing severity). 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.

15.1.1.2. Relationship to Trial Medication

A related TEAE is defined as a TEAE with a relationship to trial medication ticked “yes” according to the investigator. TEAEs with a missing relationship to study medication will be regarded as related to trial medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship (TEAE with a relationship to trial medication ticked “yes”) to trial medication will be used in the corresponding relationship summaries.

15.1.2. 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. All SAEs as recorded in the

eCRF will be listed.

15.1.3. ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to Death are those events which are recorded as "Results in death" on the Adverse Events page of the eCRF. A summary of subjects with TEAEs leading to death will be presented in overview summary. All AEs leading to Death as recorded in the eCRF will be listed.

15.1.4. ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

An overall summary of the number of subjects and percentages within each of the categories described in the sub-sections below will be provided.

The risk difference between both treatment groups will be displayed together with its 95% confidence interval (CI).

The SAS code below will be used to produce exact unconditional CI for risk difference:

```
PROC FREQ data= Data;
     TABLES trt*aesi_overall;
     EXACT riskdiff(method=score);
     WEIGHT count;
RUN;
```

In addition, risk ratio will be displayed together with associated 95% exact confidence interval.

Risk ratio will be defined as: (**a**/(**a+b**))/(**c**/(**c+d**)).
Where **a** is the number of subjects with AESI within treatment group, **a+b** is the total number of subjects in treatment group, **c** is the number of subjects with AESI within treatment, **c+d** is the total number of subjects in treatment group.

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

```
PROC FREQ data=data_AESI;
      TABLES trt*aesi_overall;
      EXACT relrisk(method=score);
      WEIGHT count;
RUN;
```

15.1.4.1. 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.

Number of subjects, percentages and number of events of Treatment Emergent AESI reported by investigators by SOC and PT table will be prepared.

15.1.4.2. Serious Infections

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

Serious infections are:

- AEs which are both infections and SAEs as reported on the Adverse Events page of the eCRF.
- AEs which are both infections and identified by 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.

Number of subjects, percentages and number of events of Treatment Emergent Infections by SOC and PT tables will be prepared.

Number of subjects, percentages and number of events of Treatment Emergent Serious Infections by SOC and PT tables overall will be prepared.

Serious Infections will be listed. The listing will include the “Adverse Event of Special Interest” equal to “Yes” and the “Is the AE an infection?” equal to “Yes” information from the Adverse Events page of the eCRF as flags.

15.1.4.3. Hypersensitivity Reactions

Hypersensitivity reactions adverse events 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.

Number of subjects, percentages and number of events of Treatment Emergent Hypersensitivity reactions by SOC and PT tables will be prepared.

Hypersensitivity reactions 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.

15.1.4.4. 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 15.3.2).

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.

Number of subjects, percentages and number of events of Treatment Emergent DILI by SOC and PT tables will be prepared.

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.

15.1.4.5. Injection-site Reactions

Injection-site reactions are those events recorded within the following subsearches of the BIcMQ "Administration site reactions" (narrow):

- Administration site reactions NEC (subsearch 1)
- Application and instillation site reactions (subsearch 2)
- Infusion site reactions (subsearch 4)
- Injection site reactions (subsearch 5)

Number of subjects, percentages and number of events of Treatment Emergent Injection-site reactions by SOC and PT tables will be prepared.

Injection-site reactions will be listed.

15.1.4.6. Anaphylactic Reactions

Anaphylactic reactions are those events recorded as MedDRA code in the pre-defined 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.

Number of subjects, percentages and number of events of Treatment Emergent Anaphylactic reactions by SOC and PT tables will be prepared.

Anaphylactic reactions 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.

15.1.5. NON-SERIOUS TREATMENT EMERGENT AES

Non-serious TEAEs are those events for which the investigator ticked "No" to the item "Is this a serious adverse event?" on the Adverse Events page of the eCRF.

Frequency of subjects, number of events and incidence of subject with non-serious TEAEs will be presented by SOC and PT, if preferred term total incidence >5%.

15.1.6. OTHER SIGNIFICANT AES

Other significant AEs are not applicable in this single-dose trial as discontinuation, withdrawal or dose reduction cannot happen.

15.2. DEATHS

If any subjects die during the trial as recorded on the "End of trial visit" page of the eCRF, the information will be presented in a summary table and a data listing based on the RND set.

15.3. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this trial for Serum chemistry, Hematology, Coagulation, and Urinalysis. A list of laboratory assessments performed at screening, admission (Day -1), Day 8, Day 22 and Day 57 is included in APPENDIX 3.

Presentations will use SI 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 and single 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 (including IGRA results) will be listed.

In case the results of a laboratory parameter are reported in different units, depending on the site who performed the measurement, and no conversion factor between the two units is available, the laboratory parameter will be analyzed by site.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Shift from baseline category (Low / Normal / High) by visit (all parameters except urinalysis parameters)
- Shift from baseline category (Negative / Positive) by visit (for urinalysis parameters)
- Incidence of possible Hy's law subjects

- Incidence of possible DILI
- The time course of ALT, AST and total bilirubin (TBL) for all possible Hy's law subjects, all parameters shown on a logarithm to base 10 scale of the multiple of the upper limit of normal (ULN) (Y axis) versus days since treatment start (X axis)
- Scatter plots for Evaluation of Potentially Drug-Induced Liver Injury:
    - log ALT on the X axis and log TBL on the Y axis, both shown on a logarithm to base 10 scale of the multiple of the ULN
    - log AST on the X axis and log TBL on the Y axis, both shown on a logarithm to base 10 scale of the multiple of the ULN

15.3.1. 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
- 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 >=3xULN)

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):
    - Category 1 : AST and/or ALT ≥3 times ULN and TBL ≥2 times ULN within the same sample
    - Category 2 : marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

15.3.2. 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: 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.

15.3.3. OTHER SAFETY LABORATORY EVALUATIONS

15.3.3.1. Pregnancy test

Descriptive table will present pregnancy results for females overall on SAF.
The pregnancy results will be listed as well on ENR.

15.4. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) 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").

In case of multiple assessments at the same date, the evaluation with the worst result is taken into account.

15.5. VITAL SIGNS

The following Vital Signs measurements will be reported for this trial:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (ºC)
- 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 time points at one visit, the pre-administration data will be considered or the last available measurement at a specific visit (if pre-administration data is not applicable) will be used for summary tables.

15.6. PHYSICAL EXAMINATION

Physical examination findings are required to be reported as relevant medical history/baseline condition or as adverse event. No separate listing or analysis of physical examination findings will be prepared.

15.7. OTHER SAFETY ASSESSMENTS

15.7.1. IMMUNOGENICITY EVALUATION

All outputs for Immunogenicity will be based on the SAF. There will be no inferential statistical comparisons between the treatment groups for immunogenicity data.

The following summary tables will be provided for immunogenicity data:

- Number and frequency of subjects with the following anti-drug antibody (ADA) / neutralizing anti-drug antibodies (nAbs) sampling results, by visit (baseline, Day 22, Day 57 and overall):
    - Negative
    - Positive
    - Total reportable (= sum of Negative and Positive)
    - Not Reportable (=no sample available or invalid sample)
    - Total (= sum of Total Reportable and Not Reportable)
- Descriptive statistics of ADA titers will be provided by visit (baseline, Day 22, Day 57 and overall), when available

The ADA and nAb results will be listed as well.

Following figures will be generated:

- Time course of ADA development (percent positive subjects) over time for all treatments
- Box plot (with whiskers) of titer within ADA positive subjects over time: at baseline, Day 22, and Day 57.
- Box plot (with whiskers) of titer within ADA positive subjects at each ADA timepoint (multiple graphs; baseline, Day 22, and Day 57)
- Time course of nAb development (percent positive subjects) over time (by planned visit day) for all treatments

15.7.2. LOCAL TOLERABILITY

Outputs for local tolerability will be based on the SAF.

The number and percentage of subjects with injection site reactions (assessed at Day 1 from the time of the injection until Day 2) will be summarized by treatment for each injection site reaction.

The number of patients with at least one injection site reaction post-administration will also be reported.

All injections site reactions will be listed.

16. PHARMACOKINETIC DATA

All outputs for pharmacokinetic outcomes will be based on the PKS.

PK analysis constitutes the primary objective of this trial to compare BI 695501 administration via PFS *vs* AI.

16.1. PRIMARY PHARMACOKINETIC

16.1.1. PHARMACOKINETIC VARIABLES & DERIVATIONS

The primary endpoints are:

- AUC_{0-1368} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 1368 hours after dose)
- C_{max} (maximum measured concentration of the analyte in plasma)
- $AUC0_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity) based on observed concentration at time of last measurable concentration

No secondary endpoints for PK are defined.

[redacted]

[redacted]

The PK parameters will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' [001-MCS-36-472].

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

If a pre-dose concentration value is greater than 5% of C_{max}, the subject's PK data will not be included in any statistical evaluations, in accordance with international guidance. The individual PK parameters of such a subject will be calculated and listed separately. These PK parameters and observed concentrations will not be included in descriptive statistics. If a pre-dose concentration is above the limit of quantification (BLQ), but less than or equal to 5% of the subject's C_{max} value, the subject's data, without any adjustments, will be included in all PK measurements and calculations.

16.1.2. Missing Data Methods for Primary Pharmacokinetic Variables

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

For the non-compartmental analysis, concentration data identified with NOS (no available sample), NOR (no valid result) or NOA (not analyzed) will generally not be considered. Concentration values in the lag phase identified as BLQ will be set to zero. All other BLQ values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

Descriptive statistics of parameters and concentrations are calculated only when a parameter value is available for at least 2/3 of the treated individuals. If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead. PK parameters that cannot be determined will be identified as "not calculated".

16.1.3. Analysis of Pharmacokinetic Variables

The primary PK endpoints will be evaluated using boxplots (linear and log-scale) for prefilled syringe versus autoinjector administration of BI 695501. In addition, scatterplots will be produced to examine the primary PK endpoints using baseline body weight as a continuous variable.

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

[redacted]

17. REFERENCES

001-MCS-36-472: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.

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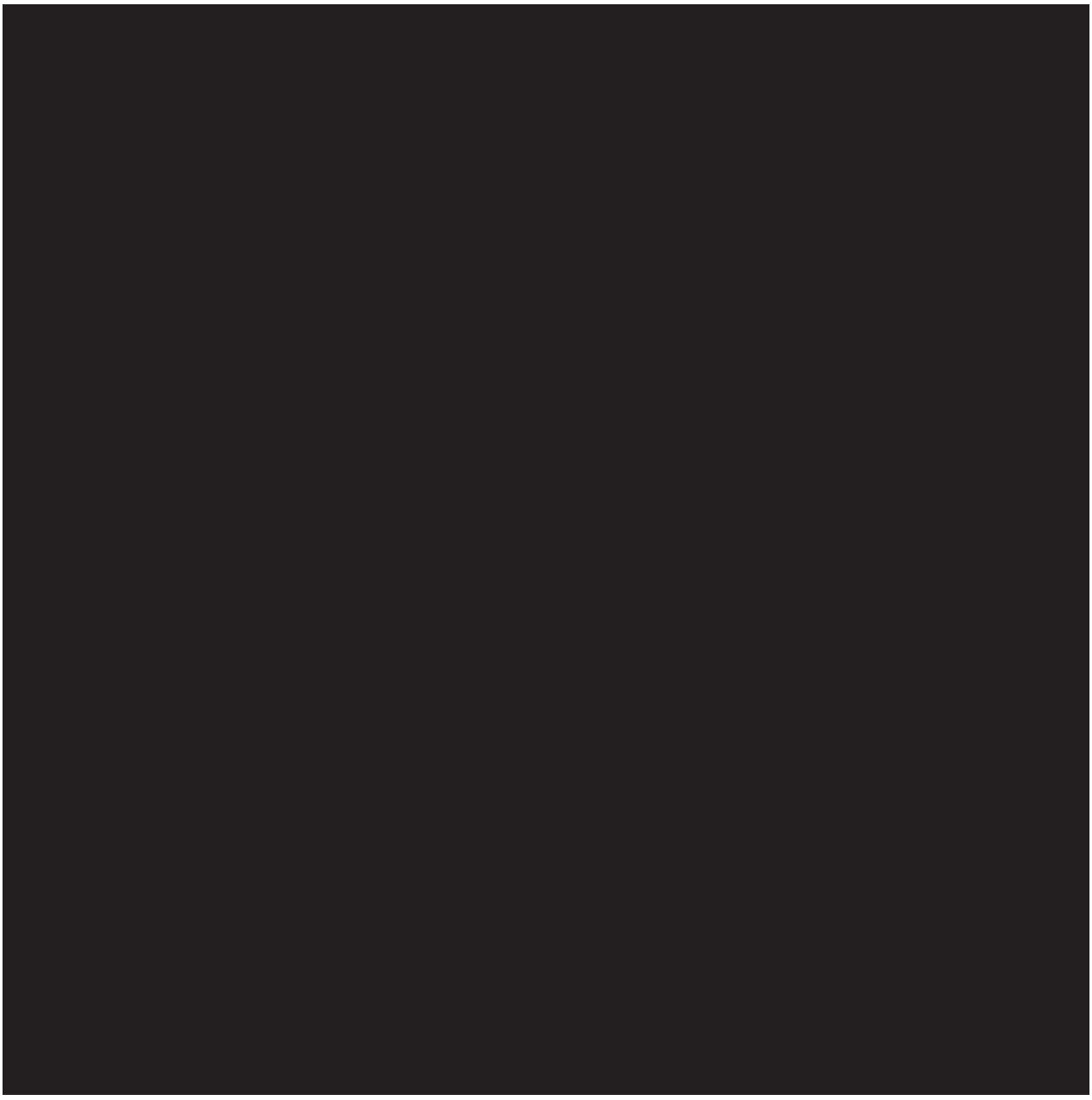

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