STATISTICAL ANALYSIS PLAN

1297-0015

RELATIVE BIOAVAILABILITY OF 40 MG/0.4 ML OF BI 695501 COMPARED TO 40 MG/0.8 ML OF BI 695501 FORMULATION FOLLOWING SINGLE SUBCUTANEOUS ADMINISTRATION IN HEALTHY MALE AND FEMALE SUBJECTS (A DOUBLE BLIND, RANDOMIZED, SINGLE-DOSE, PARALLEL-ARM STUDY)

AUTHOR: [redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - AUTHORS

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - APPROVAL

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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MODIFICATION HISTORY

Listed below are modifications made to the SAP after the signed approval(s).

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	30SEP2022	[redacted]	Not Applicable – First Version

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1. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. This trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

This document describes the rules and conventions to be used in the presentation and analysis of safety, pharmacokinetics (PK) and [redacted] data for Protocol 1297-0015. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This TSAP is based on protocol version 1.0, dated 26 November 2021.

This TSAP is developed using the [redacted] statistical analysis plan templates. The operating procedures (SOPs) and programming standards of the Sponsor will be followed for this study.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The main objective of this trial is to investigate the relative bioavailability of 40 mg BI 695501 100 mg/mL (test) versus 40 mg BI 695501 50 mg/mL (reference) following single subcutaneous administration.

2.2. FURTHER OBJECTIVES

Further objectives are the evaluation and comparison of additional pharmacokinetic parameters between the treatments and assessment of safety and tolerability.

3. STUDY ENDPOINTS

3.1. PRIMARY ENDPOINTS

The following pharmacokinetic parameters will be determined for 40 mg BI 695501 100 mg/mL and 40 mg BI 695501 50 mg/mL:

- AUC_{0-1344} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 1344 hours after dose administration)
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

3.2. FURTHER ENDPOINTS

[redacted]

3.2.3. SAFETY AND TOLERABILITY ENDPOINTS

Safety and tolerability of 40 mg BI 695501 100 mg/mL and 40 mg BI 695501 50 mg/mL will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination or 12-lead ECG)
- Safety laboratory tests
- Local tolerability
- Vital signs (BP, PR)

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

The trial will be performed as a randomized, single-dose, double blind, parallel arm trial in healthy male and female subjects aged ≥ 18 to ≤ 55 years.

It is planned to include 200 healthy male and female subjects into the trial to ensure at least 190 subjects for the primary analysis. Subjects will be randomly assigned to receive one dose of either BI 695501 40 mg/0.4 mL (T) or BI 695501 40 mg/0.8 mL (R). All study drugs will be administered by subcutaneous injection.

The trial will consist of a Screening period of up to a maximum of 28 days. The subject will check-in to the trial center on Day -1, will be dosed on Day 1. All subjects will remain in the clinic until day 2 after dosing. The subject will then return to the clinic for 13 ambulatory visits on Days 3, 4, 5, 6, 7, 8, 10, 15, 22, 29, 36, 43 and 57 (e.o.t.).

Additionally, all AEs, regardless of relatedness, will be collected until 10 weeks after the administration of trial medication. Adverse events not fully resolved at the Safety Follow-up 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.

4.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 6.1 and 6.2 of the protocol.

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

There are no changes in the analysis plans relative to the study protocol.

5. PLANNED ANALYSES

5.1. INTERIM ANALYSIS

There are no formal interim analyses planned for this study.

5.2. FINAL ANALYSIS

All final, planned analyses identified in this TSAP will be performed by [redacted] Biostatistics (excluding PK descriptive analysis) 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, determination of analysis sets, database lock and unblinding of treatment.

6. 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.

6.1. ALL SUBJECTS ENROLLED SET [ENR]

The all subjects enrolled set will contain all subjects who provide informed consent for this study. Subjects in this population will be used for disposition summaries.

6.2. ALL SUBJECTS RANDOMIZED SET [RND]

The all subjects randomized 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.

6.3. SAFETY ANALYSIS SET [SAF]

The safety analysis set will contain all subjects who were randomized and treated with study drug and will be analyzed according to treatment received. Subjects in this population will be used for all safety, dosing and demographic summaries.

6.4. PHARMACOKINETIC ANALYSIS SET [PKS]

The Pharmacokinetic Set (PKS) will consist of all randomized subjects who receive the single dose of trial medication, 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 Cmax 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 subcutaneous administration or suggesting extreme values (high or low), then these values and/or profiles will be excluded from the PK evaluation.

7. GENERAL CONSIDERATIONS

Derivation of the PK parameters for BI 695501 in plasma, and the PK summaries and data listings, will be the responsibility of the clinical pharmacokineticist at BI. The safety and [redacted] summaries and data listings will be the responsibility of the study biostatistician at [redacted].

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct

7.1. SUMMARY STATISTICS

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), median, interquartile range (IQR calculated as third quartile [Q3] minus first quartile [Q1]), minimum, and maximum values. In addition, 10^{th} percentile (P10), 90^{th} percentile (P90), coefficient of variation (CV%), geometric mean (gMean) and geometric CV% (gCV%) will also be presented for PK concentration data and all PK parameters, where applicable.

7.2. TREATMENT SUMMARIZATION

In general, data will be presented for each treatment group. Data for all study subjects combined will also be presented when appropriate.

7.3. PRECISION

Safety variables (ie, clinical laboratory values, and vital signs), including derivations thereof, will be reported to the same precision as the source data.

For the reporting of descriptive statistics, the minimum and maximum values will be presented to the same precision as the source data (base precision); base precision+1 for the mean, median and confidence intervals (CIs); and base precision+2 for the SD and IQR (see APPENDIX 1). Percentages will be presented with one decimal point.

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

For the reporting, individual and descriptive statistics of PK concentrations and parameters will be presented with three significant digits. Descriptive statistics includes N, gMean, gCV%, mean, CV%, SD, minimum, P10, Q1, median, Q3, P90 and maximum. P-values, if any, shall be reported according to the convention described in APPENDIX 1.

7.4. 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 study medication administration, (Day 1 is the day of the study medication administration), and 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 start date then:

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

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

Study Day = (date of event – reference start 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.

7.5. BASELINE

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

7.6. 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.

7.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value (after baseline) – Baseline Value

7.8. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries and listings provided by [redacted] will be generated using SAS version 9.4 or higher ([redacted]). Non-compartmental pharmacokinetic parameter calculations will be performed using Phoenix® WinNonlin® 8.1 or higher ([redacted]) and SAS version 9.4 or higher. Table, listing and figures will be prepared using the same versions of SAS.

8. STATISTICAL CONSIDERATIONS

8.1. MISSING DATA

Missing safety data will not be imputed.

Missing PK concentrations will be handled as described in Section 17.1.2 of this analysis plan.

9. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this TSAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by [redacted] Biostatistics.

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study. Subject disposition will be tabulated for each study treatment and for all subjects overall with the number of subjects who are screened, screen failure (defined as withdrawn from trial prior to randomization), randomized, randomized but not treated, completed treatment (assessed at Day 1), completed the trial (assessed at Day 57), prematurely discontinue, reason for early discontinuation, entered safety follow-up, completed safety follow-up, discontinue from safety follow-up and reason for early discontinuation from safety follow-up. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each subject.

A summary table will be produced with the number and percentage of subjects in each analysis sets.

Protocol violations relevant for primary PK analysis (as defined in section 6.4) 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

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Individual subject demographics and baseline characteristics will be presented for the RND, SAF and PKS. 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.

Demographic and other baseline characteristics such as age, sex, childbearing status, race, ethnicity, height, weight, body mass index (BMI), smoking status and alcohol status will be summarized and tabulated by treatment and for all subjects overall. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex, childbearing status, race, ethnicity, smoking status and alcohol status. No statistical testing will be carried out for demographic or other baseline characteristics.

12. PROTOCOL DEVIATIONS

12.1. DEVIATIONS RELATED TO STUDY CONDUCT

A deviation from a protocol occurs when Investigator site staff or a study subject does not adhere to the protocol's stipulated requirements, whether inadvertently or planned. Protocol deviations will be listed including a classification of minor or major and important or not important as determined by clinical staff. A summary table will be produced for protocol deviations relevant for PK evaluation.

Important protocol deviations will be reviewed also by the study pharmacokineticist and biostatistician prior to unblinding to identify deviations which have the potential to affect the pharmacokinetic results.

12.2. DEVIATIONS RELATED TO PK ANALYSIS

Changes to the procedures or events, which may impact the quality of the PK data, will be considered significant protocol deviations and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing on the day of PK sampling. In the case of a significant protocol deviation or event, PK data collected during the affected treatment period will be excluded from the study results. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviations from blood collection times.

13. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History coded using MedDRA Version 25.0 will be presented for the safety analysis set.

Surgical and Medical history will be listed and summarized by SOC and preferred term for each treatment and all subjects overall.

14. MEDICATIONS

Medication usage coded using the WHO Drug Dictionary Version March 2022 will be presented for the safety analysis set.

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.

- 'Prior' medications are medications which started and stopped prior to the single dose of study 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).

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.

15. STUDY MEDICATION EXPOSURE

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

A listing will be created with the randomisation number and study medication injection details.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

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

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 25.0 or higher. SOCs will be sorted by internationally agreed European Medicines Agency (EMA) SOC order (refer to APPENDIX 3), 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 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.

16.1.1. 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.

16.1.1.1 Intensity

Intensity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the single 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.

16.1.1.2 Relationship to Trial Medication

A related TEAE is defined as a TEAE with a causal relationship between the event and the trial drug ticked "Related" 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 causal relationship between the event and the trial drug ticked "Related") to trial medication will be used in the corresponding relationship summaries.

16.1.2. 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.

16.1.3. 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.

16.1.4. 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.

16.1.4.1 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.

16.1.4.2 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.

16.1.4.3 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.

16.1.4.4 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 16.3.1).

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.

16.1.4.5 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)
- 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.

16.1.4.6 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.

16.1.5. 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%.

16.1.6. OTHER SIGNIFICANT AEs

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

16.2. 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.

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 performed at screening, admission (Day -1), Day 10, Day 22 and Day 57 is included in section 5.2.3 of protocol.

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 7.6. 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.

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

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
- 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

16.3.2. Laboratory Reference Ranges and Markedly Abnormal Criteria

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

- Low: 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. Other Safety Laboratory Evaluations

16.3.3.1 Pregnancy test

Descriptive table will present pregnancy results for females overall on SAF.

The pregnancy results will be listed as well on ENR.

16.4. 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.

16.5. VITAL SIGNS

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

- Systolic and Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (°C)
- Weight (kg)

The handling of retests, unscheduled and end of trial measurements is described in Section 7.6.

The summary of actual and change from baseline by visit will be provided for vital sign data.

16.6. 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.

16.7. OTHER SAFETY ASSESSMENTS

[redacted]

[redacted]

16.7.2. 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, prior to discharge from the trial site) 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.

17. PHARMACOKINETIC DATA

All outputs for pharmacokinetic outcomes will be based on the PKS. BI 695501 plasma concentrations and PK parameters will be listed with descriptive statistics. Individual plasma concentrations, as well as (geometric) mean plasma concentrations will be plotted versus time (linear and semi-log scale). Individual and gMean PK parameters for test and reference treatment will also be part of the figures. Boxplots with whiskers will be displayed for the primary endpoints.

PK analysis constitutes the primary objective of this trial to compare two formulations of BI 695501 administration [40 mg / 0.4 mL (T) vs 40 mg / 0.8 mL (R)].

17.1. PRIMARY PHARMACOKINETIC ANALYSIS

17.1.1. PHARMACOKINETIC VARIABLES & DERIVATIONS

The primary endpoints are:

- AUC0-1344 (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 1344 hours after dose)
- AUC0-∞ (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
- Cmax (maximum measured concentration of the analyte in plasma)

No secondary endpoints for PK are defined.

[redacted]

17.1.2. 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".

17.1.3. Analysis Of Pharmacokinetic Variables

The PK parameters will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' [according to the relevant SOP of the Sponsor].

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 Cmax, 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 Cmax value, the subject's data, without any adjustments, will be included in all PK measurements and calculations.

The primary PK endpoints will be plotted using boxplots with whiskers for PK parameters after administration of test product (40 mg BI 695501 100 mg/ml, 0.4 ml) and administration of the reference product (40 mg BI 695501 50 mg/ml, 0.8 ml).

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" according to the SOP of the sponsor.

17.1.4. Primary Analysis For Pharmacokinetic Variables

Relative bioavailability of 40 mg/ 0.4 ml BI 695501 formulation (Test, T) compared to 40 mg/ 0.8 ml of

BI 695501 formulation (Reference, R) will be estimated by the ratios of the geometric means (T/R) for the primary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided.

The primary PK endpoints for BI 695501 will be estimated using an analysis of covariance (ANCOVA) model on the logarithmic scale (natural logarithm) with effects for treatment, location of trial medication injection and baseline body weight (continuous).

The ANCOVA model is described by the following equation:

$y_{kjm} = \mu + \tau_k + \varphi_j + \beta * weight_{km} + e_{kjm}$, where

y_{kjm} = logarithm of PK parameter measured on subject m receiving treatment k at location j,

μ = the overall mean,

τ_k = the k-th treatment effect, k = 1, 2 (1=T (BI 0.4 mL) , 2=R (BI 0.8 mL)),

φ_j = the j^{th} effect of location (thigh, abdomen), j= 1, 2,

β = the slope parameter for the baseline body weight covariate,

$weight_{km}$ = baseline body weight of subject m receiving treatment k, and,

e_{kjm} = the random error associated with the m-th subject who received in location j treatment k,

where $e_{kjm} \sim N(0, \sigma_k^2)$ are independent random variables.

The following SAS code will be used:

(M1)
```
PROC MIXED data= ADPP<restricted to parameter> METHOD=REML;
  CLASS TRTP(ref="R") Location;
  MODEL AVAL = TRTP Location BASE_WEIGHT /DDFM=KR;
  LSMEANS   TRTP;
  ESTIMATE 'BI 695501 T versus R'  TRTP 1  -1 /alpha=0.1;
```
RUN;

For model (M1), AVAL refers to the PK endpoint value on the logarithmic scale.

For each PK endpoint, (M1) estimates the difference between the means for log(T)-log(R) by the difference in the corresponding adjusted means (least-squares means), and a two-sided 90% CI based on the t-distribution will be computed.

These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for the corresponding ratio of geometric means (T/R) for each PK endpoint.

A forest plot will be produced to report the results of the primary analysis.

18. REFERENCES

Not Applicable.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

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, P10, Q1, Q3, P90 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:

o Minimum and maximum: N

o Mean, gMean, median, gCV% and CV%: N + 1

o 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 semi-colon.
- 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 RTF 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.
- Boxplots will display whiskers extending from P10 to first quartile and from 3rd quartile to P90.

DATES & TIMES

Depending on data available, dates and times will take the format yyyy-mm-dd; times will take the format hh:mm:ss; combined dates and times will take the format yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

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

Treatment Group
BI 695501 40 mg/0.4 mL
BI 695501 40 mg/0.8 mL

PRESENTATION OF VISITS

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

Long Name (default)	Short Name
Screening (Day -28 to -2)	Scrn
Day -1	D -1
Day 1	D 1
Day 2	D 2
...	
Day 57	D 57
Day 70	D 70

PRESENTATION OF NOMINAL TIMES

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

Long Name (default)	Short Name
x hour(s)	x h

LISTINGS

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

- randomized treatment group (or treatment received if it's a safety output)
- subject ID,
- date including Study day (where applicable),

- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labelled 'Not Randomized'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

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 study med start date	Known Partial Missing	Not TEAE
Partial, could be on or after study 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 study med start date or if day and month are missing and year of start date is the same as for study med start date. In the later cases, the study 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.

START DATE	STOP DATE	ACTION
		If start date <= stop date, then : If stop date < trial med start date, then not TEAE If start date > trial med end date +70 days, then not TEAE If stop date >= trial med start date and start date <= trial med end date +70 days, then TEAE If start date > stop date, then : Consider the start and stop dates as Missing and apply the algorithms for missing start date
	Missing	Assumed TEAE
Missing	Known	If stop date < trial med start date, then not TEAE If stop date >= trial med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < trial med start date, then not TEAE If stop date >= trial med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

Partial date to be imputed as:

Start date	Earliest possible date	first day of month if day unknown or 1st January if day and month are unknown
Stop date	Latest possible date	last day of month if day unknown or 31st December if day and month are unknown

General rules:

If stop date < trial med start date, assign as prior

If start date>= trial med start date and start date <= end of trial date on Day 70, assign as concomitant

If Missing stop date : (Rules 2)

If stop date is missing could never be assumed a prior medication

If start date <= end of trial date on Day 70, assign as concomitant

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

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

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

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

APPENDIX 4. **BIcMQs**

BIcMQs identification is based on a separate external excel file named:

- BIcMQ_25.0_Administration_site_reactions

MedDRA version 25.0 or higher will be used.