TRIAL STATISTICAL ANALYSIS PLAN

c33844082-01

BI Trial No.:	1368-0043
Title:	An open-label phase I trial to assess pharmacokinetics and safety of single subcutaneous doses and single intravenous doses of BI 655130 in healthy Chinese male and female subjects (single doses, open-label study in parallel-group design). (including Protocol Amendments No.1-4 [c27981303-05])
Investigational Product:	BI 655130 (Spesolimab)
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	09 MAR 2021 SIGNED
Version:	1

1. TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC_{0-tz}	Area under the concentration-time curve of the analyte in serum over the time interval from 0 to the last quantifiable drug concentration
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BLQ	Below limit of quantification
BMI	Body mass index
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
CSD	Company standard displays
CV	Arithmetic Coefficient of Variation
DBLM	Database Lock Meeting
DILI	Drug induced liver injury
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
LLOQ	Lower limit of quantification
LLT	Lower Level Term
IQRMP	Integrated Quality and Risk Management Plan
Max	Maximum
Min	Minimum
N	Number non-missing observations
P10	10^{th} percentile
P90	90^{th} percentile
PKS	PK parameter analysis set
Q1	1^{st} quartile
Q3	3^{rd} quartile
RAGe	Report Appendix Generator system

Term	Definition / description
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
SD	Standard Deviation
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TS	Treated Set
UDAEC	User Defined Adverse Events Concepts
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per ICH E9 (1), 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, randomisation.

Study data (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 6.3 or higher, [redacted]).

The statistical analyses will be performed within the validated working environment CARE, including SAS® (current Version 9.4, by [redacted]), and a number of SAS®-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP. The following changes compared to the protocol will be made:

In CTP section 7.3 the following was defined: *Important protocol deviation (IPD) categories will be specified in the Integrated Quality and Risk Management (IQRM) Plan. IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.* Due to SOP changes, the IPD categories are no longer available in IQRM plan but included in an Excel spreadsheet (3). The IPD categories originally defined in IQRM plan were transferred to the IPD specification file. Minor changes regarding the IPD categories were performed only.

In CTP section 5.2.6.1.4 the following definition was used for an AE of special interest: *Severe infections (according to RCTC grading in ISF)*. As it is a healthy volunteer study, no RCTC grades were applied, therefore the definition 'Severe infections (according to AE intensity grades as ticked in eCRF)' was used for analysis.

In CTP section 7.3, the following definition was included by mistake:

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*

As route of study drug administration is sc or iv, emesis has no effect on PK evaluability and will not be considered for PK analysis.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary objective of this trial is to investigate PK, including dose proportionality, following single IV and SC doses of Spesolimab in healthy Chinese subjects. Primary endpoints are $AUC_{0-\infty}$ and C_{max} of Spesolimab.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:
The occurrence of treatment-emergent AEs (e.g. number of subjects with treatment-emergent AEs).
The occurrence of drug-related AEs (e.g. number of subjects with drug-related AEs).

Safety and tolerability of Spesolimab will be assessed based on:

- *Safety laboratory parameters*
- *12-lead ECG*
- *Vital signs (blood pressure [BP], pulse rate [PR], respiratory rate [RR], body temperature)*
- *Immunogenicity (ADA)*

5.4 OTHER VARIABLES

There are the following other parameters which will be listed and tabulated:
Subject information:

- Informed consent
- Relevant medical history
- Concomitant therapy
- Inclusion/Exclusion criteria

Demographic data:

- Gender
- Height
- Weight
- Smoking history
- Alcohol history
- Race
- Ethnicity

Age [years] will be determined as the difference between year of informed consent and year of birth.

BMI will be calculated as weight [kg] / (0.01 * height [cm])^2.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on investigational products, assignment of treatment sequences and selection of doses, please see CTP, Sections 3 and 4.

The study will be performed as a single dose, open-label non-randomized study in parallel-group design.

It is planned to include up to 60 healthy male and female subjects in the trial. The subjects will be assigned to 5 groups each consisting of 10 subjects with at least 3 subjects for each gender within each dose group. The cohorts within each SC and IV dose groups will be dosed sequentially.

For details of dosage and formulation see Table 6.1:1 below.

Table 6.1: 1 Labels for treatments for use in the CTR

Dose group	Treatment		Short label
1	A	BI 655130, 450 mg, iv, once	Speso 450mg iv
2	B	BI 655130, 900 mg, iv, once	Speso 900mg iv
3	C	BI 655130, 1200 mg, iv, once	Speso 1200mg iv
4	D	BI 655130, 300mg, sc, once	Speso 300mg sc
5	E	BI 655130, 600mg, sc, once	Speso 600mg sc

The following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00h (midnight) on day of informed consent until first administration time of study drug Spesolimab))
- **On treatment**
  - **BI treatment** (separately for each treatment, ranging from the time of first administration of Spesolimab / start of infusion of Spesolimab until time of administration + REP (defined as 16 weeks) / end of infusion + REP (defined as 16 weeks))
  - **Follow-up (F/U)** (ranging from administration / end of infusion of Spesolimab + REP until 0:00h (midnight) on the day after trial completion date))

The following AE displays will be provided in the report:

Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening and Follow-up phases will not be included in this analysis.

The following totals will be provided in addition:

- a total over all on treatment phases included in this analysis ("**Total**") (Appendix 16.1.13.1.8 only)
- a total over all on treatment phases included in this analysis ("**Total iv**") (tables including iv treatment groups)
- a total over all on treatment phases included in this analysis ("**Total sc**") (tables including sc treatment groups)

Tables for ClinicalTrials.gov will be provided including both sc and iv groups.

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, the screening and follow-up period will be included and no totals will be provided.

Tables of vital signs and laboratory values will present results for the above mentioned on treatment phase.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects.

Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting and database lock meeting (RPM/DBLM). At this meeting, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes via an accompanying Excel spreadsheet.

Categories which are considered to be iPDs in this trial were defined in the integrated quality and risk management plan (IQRMP) prior to trial initiation. The IPD list was transferred into the IPD specification file (due to changes in the SOP) (3). Within this transfer some minor adaptations were done to comply with new naming conventions and categorisations. IPDs will be identified no later than in the Report Planning Meeting and the IPD categories will be updated as needed. The decision on exclusion of subjects from analysis sets will be made after discussion of exceptional cases and implications for analyses.

The iPDs will be summarised and listed.

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP: *Statistical analyses will be based on the following analysis sets:*

- *Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treatment assignment will be determined based on the (first) treatment the subjects received. The treated set will be used for safety analyses.*

- *PK parameter analysis set (PKS): This set includes all subjects in the TS who provide at least one primary PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Descriptive and model based analyses of PK parameters will be based on the PKS. It is expected that PK data from replaced subjects is not evaluable and thus replaced subjects are not expected to be part of the PKS.*

Plasma concentration data and parameters of a subject will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below).

Exclusion of a subject's data will be documented in the CTR.

Relevant protocol deviations may be

- *Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*

- *Incorrect dose of trial medication taken*

- *Use of restricted medications*

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *Missing samples/concentration data at important phases of PK disposition curve.*

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Table 6.3: 1 Subject sets analysed

	Subject analysis set	
Class of endpoint	Treated set	PKS
Analysis of PK endpoints		X
Safety parameters	X	
Demographic/baseline parameters	X	
Important protocol deviations	X	
Disposition	X	

[redacted]

6.5 POOLING OF CENTRE

This section is not applicable, because the study was performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the CTP, Section 7.4.

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035 (4)).

Missing data and outliers of PK data are handled according to BI standards (see BI-KMED-TMCP-MAN-0014) (5).

Missing baseline laboratory values will be imputed by the respective values from screening or from ambulatory visit (ptm -48:00) if available.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before first administration of Spesolimab (= value at V2 Day 1, in case no actual time is given in data).

The acceptable time windows for visits are given in the CTP Flow Chart and CTP Section 6.1.

Adherence to time windows will be checked via the consistency check listings at the RPM/DBLM.

Unscheduled measurements of laboratory data and vital signs data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

7. PLANNED ANALYSIS

If not otherwise stated, tables and listings will be done separately for IV treatment groups and SC treatment groups.

Safety analysis (refer to Section 7.8) will be performed by [redacted] and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Section 7.4.1 and Section 7.6) will also be performed by [redacted] and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK parameters and concentrations will be performed by the department [redacted] at [redacted] and will be presented in Section 15.6 of the CTR.

Descriptive data analysis of ADA will be performed by the department [redacted] at [redacted] and will be presented in Section 15.8 of the CTR.

The format of the listings and tables will follow the BI standards (see BI-KMED-BDS-HTG-0045 (6)) with the exception of those generated for PK-calculations (5).

The individual values of all subjects will be listed, sorted by treatment group, subject number, and visit.

The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

N	number non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For analyte concentrations, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

For PK parameters, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile

Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category, as well as the percentage (%) for each treatment group. Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Exclusion of PK parameters

The ADS ADPP (PK parameters) contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion, that is APEXC is equal to “Included”.

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to ‘DESC STATS’, the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’, the value can be used for further analyses based on actual times. If ACEXCO is set to ‘HALF LIFE’, the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in BI-KMED-TMCP-MAN-0014 “Noncompartmental PK/PD analyses of Clinical Studies” (5).

Preliminary and interim analysis

If required for early interaction with regulatory agency, a preliminary snapshot will be conducted once all IV subjects have completed the study. This snapshot includes the complete clinical data of the iv group, but without PK/ADA data.

Furthermore an interim lock will be conducted at a later time. This interim lock includes the complete clinical data of the iv group, inclusive PK/ADA data. An interim report for the IV analysis will be written. All analyses defined in this TSAP restricted to IV subjects will be

done for this interim analysis. For details on interim analysis, e.g. definition of topline results, please refer to Section 9.1.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.

The data will be summarised by treatment group and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the latest version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should be marked with a "No" in the respective column.

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM/DBLM.

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured sample concentrations will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM/DBLM (see Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoints

Section 7.1.3 of the CTP: *The primary endpoint as specified in Section 5.1 will be derived according to BI standards* (BI-KMED-TMCP-MAN-0014). *The analysis will be based on the PKS and will be descriptive in nature.*
For IV doses the dose proportionality of $AUC_{0-\infty}$ and C_{max} will be analysed.

Assessment of dose proportionality
Dose proportionality will be explored via graphical checks and if applicable via the power model stated below. The analysis will be performed for the PK endpoints AUC/C_{max} specified in section 5.1.

The power model describes the functional relationship between the dose level and PK endpoint on the log scale via

$$y_{km} = log\ (x_{km}) = \mu + b \cdot log\ (D_k) + e_{km}\ ,$$

where

- y_{km} *logarithm of response (PK parameter) measured on subject* m^{th} *receiving dose k,*
- μ *the overall mean,*
- β *slope parameter of linear regression line,*
- D_k *level of dose k, k=1, 2, 3,*
- e_{km} *the random error associated with the* m^{th} *subject who was administered dose k* ($e_{km} \sim N(0, \sigma^2)$ *iid).*

This equation can be fit as a linear regression model.
The slope parameter β together with its two-sided 90% confidence interval will be estimated. Perfect dose proportionality would correspond to a slope of 1. Additionally, the r-fold change $r^{\beta-1}$ *together with its 90% CI will be derived.*

Graphical displays:

A regression plot will be performed, where the logarithm of dose is depicted versus logarithm of PK endpoint, including the estimated regression line from the power model and reference line of perfect proportionality (β=1).

This analysis will be based on the PKS.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoints

Not applicable.

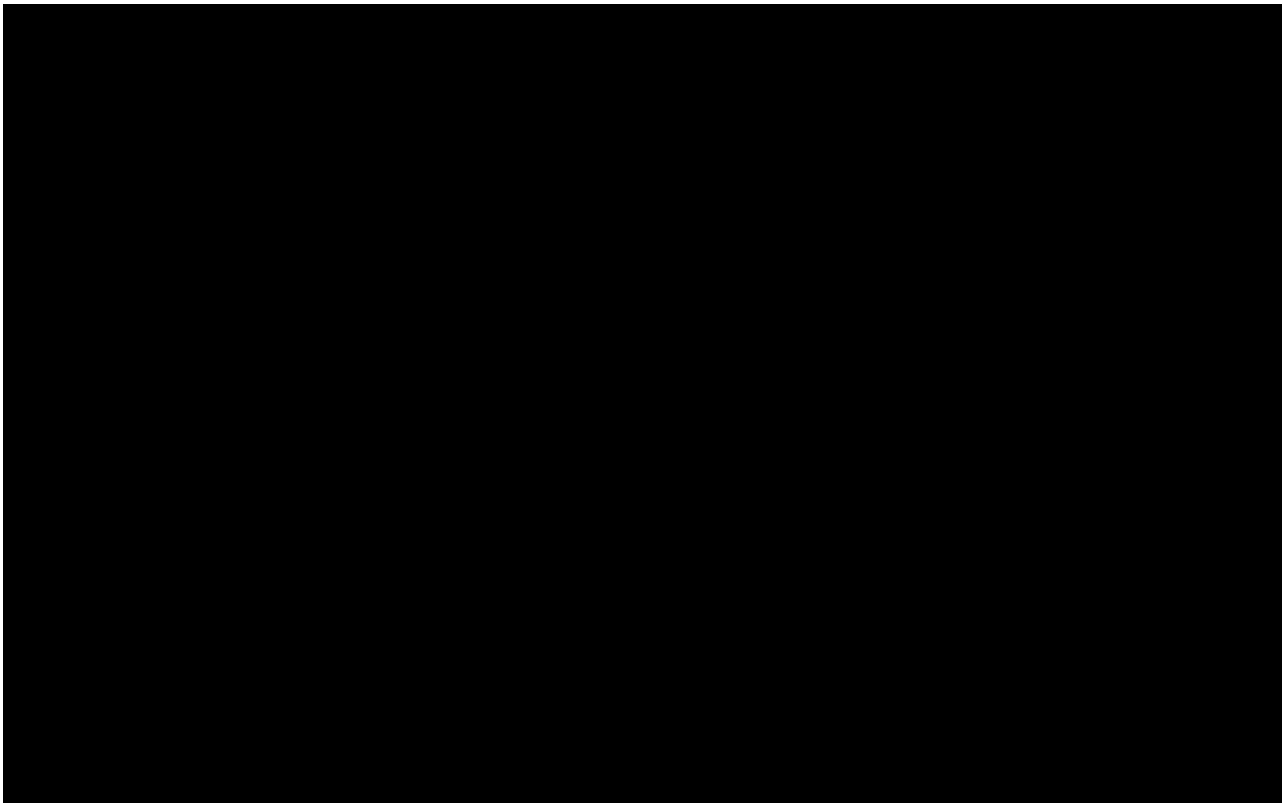
7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoints

Refer to TSAP Section 7.8.1 for a description of the analysis of adverse events.



7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

Unless stated otherwise, the safety results will be sorted by treatment group.

The safety data for treated subjects who fail to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in “Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template” [BI-KMED-BDS-HTG-0041] (8).

The standard AE analyses will be based on the number of subjects with AEs (and not on the number of AEs).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to 'screening', 'on treatment' or 'follow-up' phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1.

Section 1.2.6 of the CTP: *The residual effect period (REP) of Spesolimab is 16 weeks.*

According to the clinical study protocol, adverse events of special interest (AESI) will be analysed:

Section 5.2.6.1.4 of the CTP: *The following are considered as AESIs in this trial:*

- *Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:*
  - *an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or*
  - *ALT, and/or AST elevations ≥10-fold ULN*

  These lab findings constitute a hepatic injury alert and the subjects *showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.*

- *Systemic hypersensitivity including infusion reaction and anaphylactic reaction:*
  Any suspicion of severe infusion reaction systemic/hypersensitivity reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.1.3, R11-4890).
- *Severe infections* […]
- *Opportunistic and mycobacterium tuberculosis infections*
  These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), hepatitis B virus [HBV] reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix

schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), hepatitis C virus [HCV] progression (R17- 2617).

According to ICH E3 (9), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report.

The definition of 'other significant' AE to be used in this trial is derived by the sponsor and is based upon that according to ICH E3, and will include AEs reported as non-serious adverse events with 'action taken = Drug Withdrawn' or 'action taken = Drug Reduced'.

An overall summary of adverse events will be presented (including number of subjects with any AE, drug related AEs, serious AEs and drug related serious AEs).

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with SAEs, for subjects with drug-related AEs, patients with investigator-defined AESIs per CTP, and patients with other User-Defined Adverse Event Concepts (UDAEC) (cf. Table 7.8.1: 1 below). In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, SOC and PT.

Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Events Concepts

Important risk	*User-defined AE category*	
	Label	*Description*
Infections (serious/severe, opportunistic)	Infections ALL	Combined search strategy based on the individual UDAECs described below; the UDAEC "severe infections (investigator-defined) will be disregarded for this search
	Opportunistic infections	Narrow SMQ "Opportunistic infections"
	Tuberculosis related terms	BIcMQ "Infections": Narrow sub-search 8.2 "Tuberculosis related terms"
	Serious infections	all serious events in SOC "Infections and infestations"
	Severe infections	all events in SOC "Infections and infestations" of at least severe AE grade
	Severe infections (investigator defined)	as per tick box on the eCRF (investigator-defined)

* this is achieved by retrieving all cases found either by running subsearch 1 in narrow scope (BIcMQ search ID 32019093) or subsearch 2 (BIcMQ serach ID 32019094)

Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Events Concepts - continued

Hypersensitivity	Hypersensitivity ALL	Combined search strategy based on the three individual UDAECs described below
	Anaphylactic reaction	Narrow SMQ “Anaphylactic reaction”
	Angioedema	Narrow SMQ “Angioedema”
	Hypersensitivity	Narrow SMQ “Hypersensitivity”
Malignancies	Malignant tumours	Narrow Sub-SMQ “Malignant tumours” Narrow Sub-SMQ “Haematological malignant tumours” Narrow Sub-SMQ “Non-Haematological malignant tumours”
	Malignant skin tumours	Broad Sub-SMQ “Skin malignant tumours”
	Skin melanomas	HLT Skin melanomas (excl. Ocular)
	Non-melanoma skin cancer (NMSC)	Broad Sub-SMQ “Skin malignant tumours” excluding HLT Skin melanomas (excl. Ocular)
	Malignancies excluding NMSC	Sub-SMQ “Malignant tumours” excluding *NMSC*, whereas *NMSC* is defined above
	3-point MACE	BIcMQ 3-MACE with subsearch 1.1 narrow and subsearch 1.2 narrow *”
	Torsades de pointes	Broad SMQ “Torsades de pointes/QT prolongation”

* this is achieved by retrieving all cases found either by running subsearch 1 in narrow scope (BIcMQ search ID 32019093) or subsearch 2 (BIcMQ serach ID 32019094)

The system organ classes will be sorted by frequency, PTs will be sorted by frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [BI-KMED-BDS-HTG-0042] (10).

For continuous safety laboratory parameters, normalized values will be derived. Normalisation means transformation to a standard unit and to a standard reference range. The process of normalisation, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (10). All analyses considering multiple times of the ULN (as described below) will be based on standardized and not normalized values. For continuous safety laboratory parameters, differences to baseline will be calculated. For all outputs, the last assessment before the first randomized treatment at Day 1 is chosen as the baseline value.

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Only patients with at least one available post-baseline value will be included in the analysis of an individual laboratory parameter. Values outside the reference range as well as values defined as possible clinically significant will be flagged in the data listings.

Descriptive statistics of laboratory values and for the difference from baseline on-treatment (see Section 6.7) will be based upon standardized values and provided by visit (including summaries of the last value, the minimum value and the maximum value on treatment).

Possibly clinically significant abnormalities will be identified based on BI standard rules which are based on converted lab values and converted reference ranges, i.e. using SI units. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarize the number of patients with possibly clinically significant abnormalities. If applicable, patients having an abnormal lab value at baseline will be presented separately. A separate listing will present possibly clinically significant abnormal lab values; for each functional lab group all patient's lab values will be listed, if there exists at least one lab value with clinically significant abnormality within the group.

The frequency of patients with AST or ALT elevations ≥ 3xULN, ≥ 5xULN, ≥ 10xULN, and ≥ 20xULN will be displayed based on standardized laboratory values. To support analyses of liver related adverse drug effects, the frequency of patients with AST and/or ALT ≥ 3xULN combined with a total bilirubin ≥ 2xULN in a 30 day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase < 2xULN and ≥ 2xULN (a patient can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin elevations). The start of the 30 day time span is triggered by each liver enzyme elevation above the defined thresholds. This analysis will be based on standardized laboratory values. A graphical analysis of the ALT and total bilirubin during the on-treatment period will also be performed; the so called eDISH plot. In the graph, for each subject, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed or total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph in order to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (Hy's Law quadrant),

while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3xULN and total bilirubin < 2xULN).

Clinically relevant findings in laboratory data will be reported as adverse events if judged clinically relevant by the investigator, and will be analysed as such.
It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not (at the RPM/DBLM at the latest).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure, pulse rate and respiratory rate) based on the last value of the subject at that planned time point (or assigned to that planned time point) and including summaries of the minimum value and the maximum value on treatment. In the listing the difference from baseline will also be displayed.

Body temperature will be listed only.

Clinically relevant findings in vital signs will be reported as AEs.

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (if they pre-exist prior to trial inclusion) or will be reported as AEs (if they occurred on treatment), and will be analysed as such.

No separate ECG listing will be provided.

7.8.5 Others

Physical examination

Physical examination findings, including general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such.

No separate listing or analysis of physical examination findings will be prepared.

Local tolerability
Local tolerability will be assessed by the investigator on the basis of 'swelling', 'induration', 'heat', 'redness', 'pain', or 'other findings'. A frequency table with worst assessment by treatment group and in total will be provided.

Body weight

Body weight will be determined at screening and end of trial visit. Descriptive statistics including change from baseline will be performed by treatment group and in total.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, IDEA for CON
3.	*BI-KMED-BDS-TMP-0059: "iPD specification document (sdtm-dv-domain-specification)", template, current version, KMED.*
4.	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version; KMED.
5.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; KMED.
6.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED.
7.	*BI-KMED-TMCP-MAN-0012:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED.
8.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version; KMED.
9.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
10.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**09-MAR-21**	[redacted]	None	This is the final TSAP