TRIAL STATISTICAL ANALYSIS PLAN

c33486288-01

BI Trial No.:	1379.6
Title:	An open label, Phase I study of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours Including Protocol Amendments 1, 2 and 3 (c27190653-04)
Investigational Product(s):	BI 891065 + BI 754091
Responsible trial statistician(s):	[redacted] Phone: +[redacted]
Date of statistical analysis plan:	18 MAR 2021 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AGP	Alpha-1 Acid Glycoprotein
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
cIAP	Cellular Inhibitor of Apoptosis
CR	Complete Response
CT	Concomitant Therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug-induced Liver Injury
DLT	Dose-limiting Toxicity
ECG	Electrocardiogram
ECGPCS	Electrocardiogram Pharmacokinetic Concentration Set
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ES	Enrolled Set
HR	Heart Rate
ICH	International Conference on Harmonization
iCPD	Immune Confirmed Progressive Disease
iCR	Immune Complete Response
iPR	Immune Partial Response
iPD	Important Protocol Deviations
iRECIST	modified RECIST 1.1 for immune-based therapeutics

iSD	Immune Stable Disease
iUPD	Immune Unconfirmed Progressive Disease
MedDRA	Medical Dictionary for Regulatory Activities
msec	milliseconds
MTD	Maximum Tolerated Dose
NSCLC	Non-small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
PBMCs	Peripheral Blood Mononuclear cells
PD	Progressive Disease
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PR	Partial Response
PR interval	ECG interval from the onset of the P wave to the beginning of the QRS complex
PT	Preferred Term
QRS	Combination of the Q, R and S waves
QT	ECG interval from the beginning of the QRS complex to the end of the T wave
QTc	Generic term for QTcF and QTcB intervals
QTcB	QT interval, corrected by Bazett's formula
QTcF	QT interval, corrected by Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumours
REP	Residual Effect Period
SCR	Screened Set
SD	Stable Disease
SMAC	Second Mitochondrial Activator of Caspases
SMC	Safety Monitoring Committee
SOC	System Organ Class
StD	Standard Deviation
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO DD	World Health Organisation Drug Dictionary

3. INTRODUCTION

As per International Conference on Harmonisation E9 (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, and definition of measurements and variables.

The study was planned as a multicentre study consisting of two study parts. Part A is an open-label, BI 891065 monotherapy dose-escalation. Part B was planned to be an open-label dose-escalation of BI 891065 in combination with a fixed dose of BI 754091. In June 2020, BI decided to cancel Part B. Consequently, this TSAP will describe the analysis of Part A only.

For the primary objective of Part A of the trial, refer to Section 2 of the CTP.

This TSAP describes the analysis of all aspects of the trial. Analyses with regards to these will be described in a separate analysis plan and results will be reported in a separate report outside of the CTR. The measurements of the cytokine analyses will be included in the CTR and described in this TSAP.

In the following, study medication always refers to BI 891065 monotherapy.

SAS® Version 9.4 or higher will be used for all analyses besides pharmacokinetic (PK) analyses if not specified otherwise. Phoenix® WinNonlin® 8.1 will be used for PK analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in the CTP will be carried out.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Part A:
The primary endpoints for Part A of the trial are:

- Maximum tolerated dose (MTD)
- the number of patients with dose-limiting toxicities (DLTs) during the MTD evaluation period (first treatment cycle).

For definition of the MTD, refer to Section 2.1.1 of the CTP.

5.2 SECONDARY ENDPOINT(S)

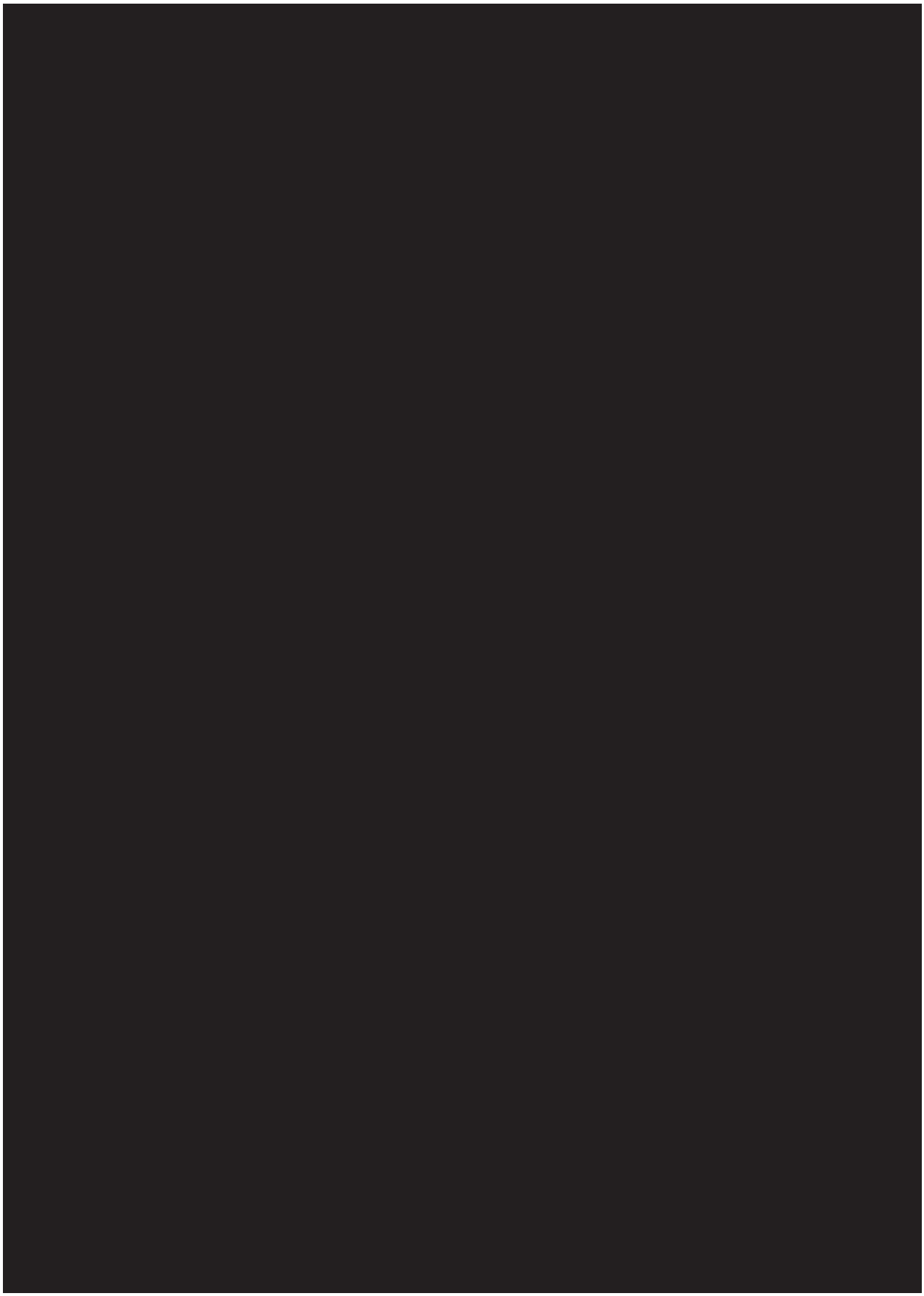
5.2.1 Key secondary endpoint(s)

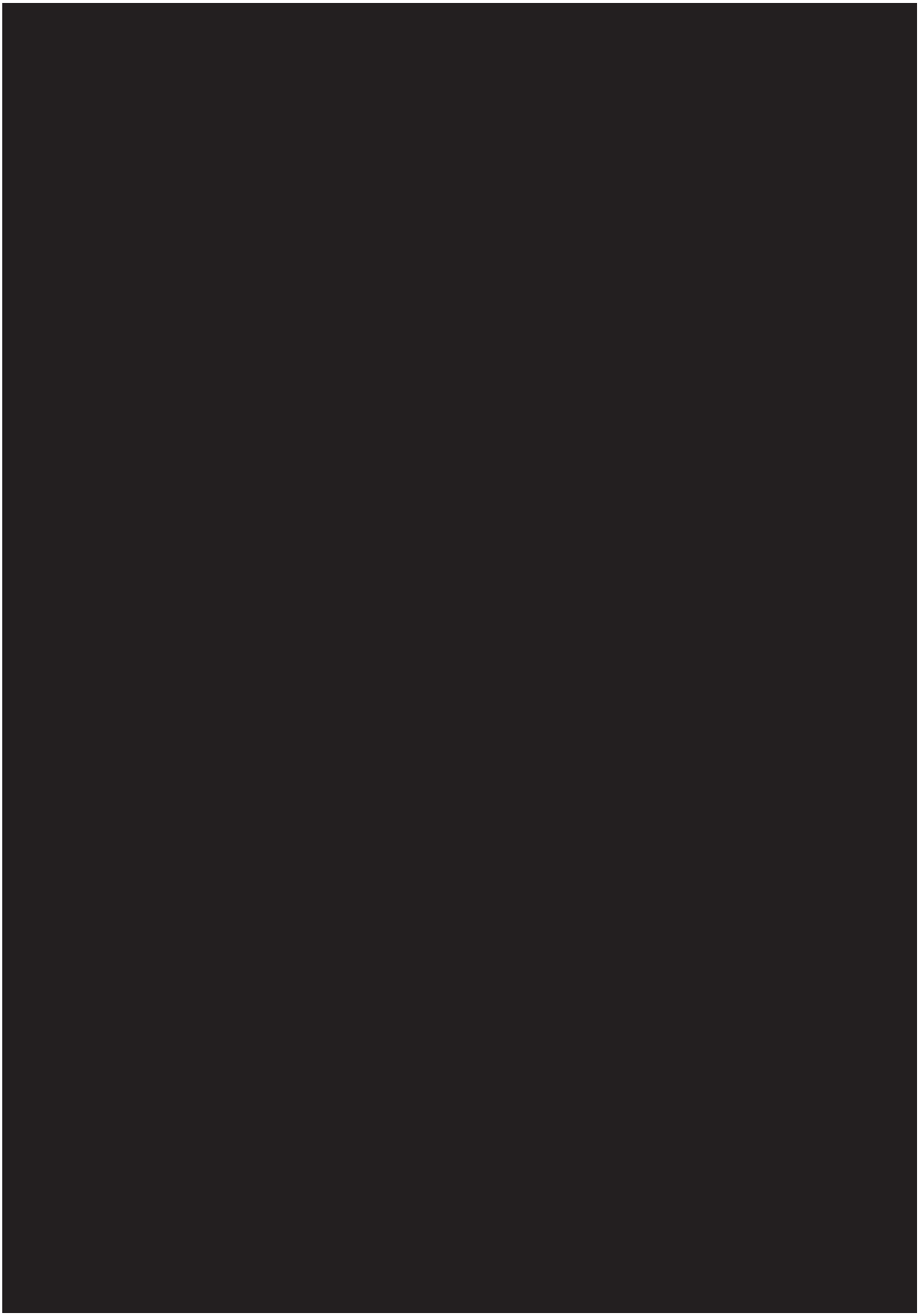
Not applicable.

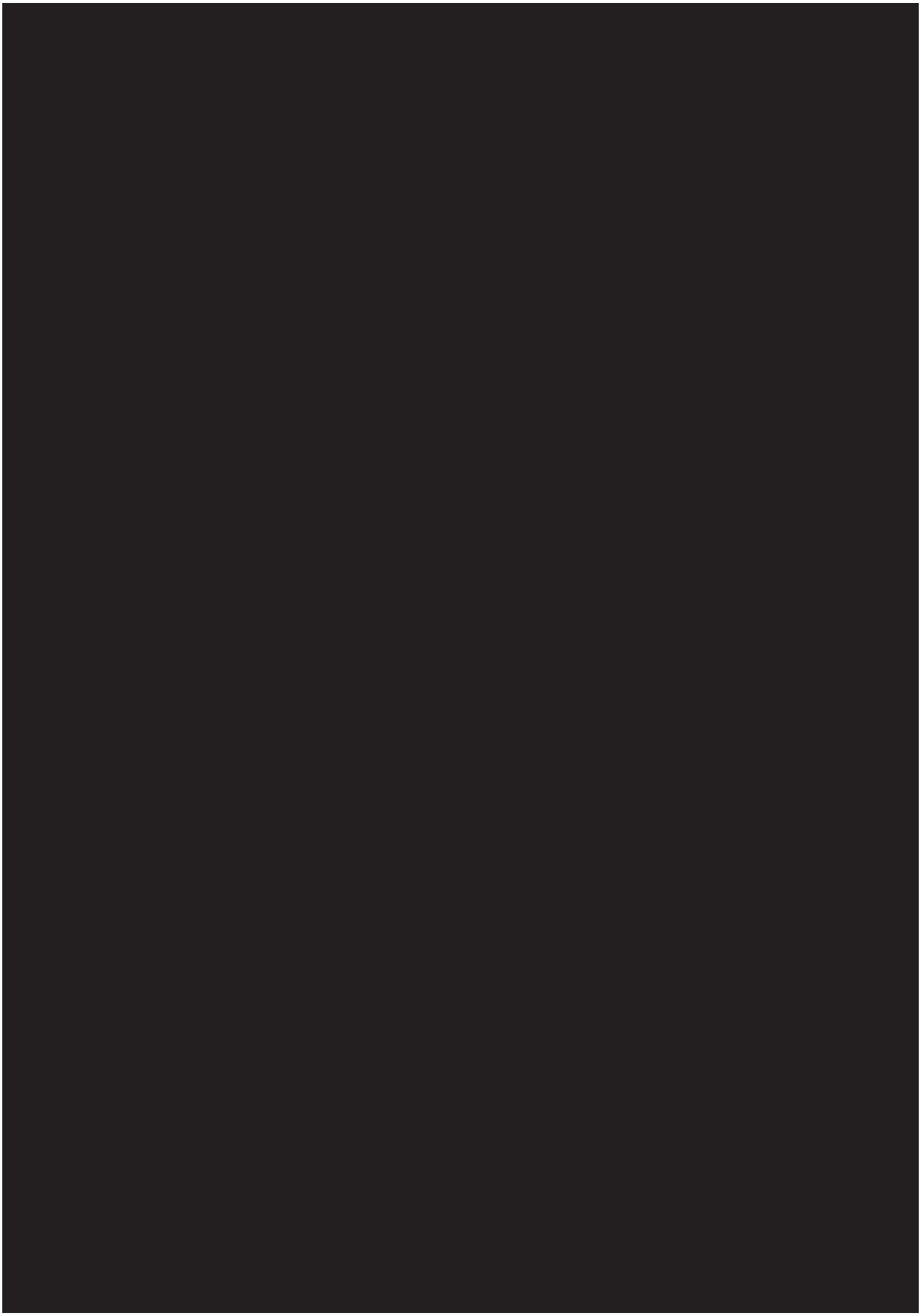
5.2.2 Secondary endpoint(s)

Part A:

- The pharmacokinetics (PK) parameters of BI 891065 will be calculated in cycle 1: $C_{max(ss)}$, AUC_{0-24} and $AUC_{\tau,ss}$ of BI 891065







6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

In Part A of this Phase I trial, treatments are not randomized. Different dose levels and dose schedule of BI 891065 monotherapy are being administered.

The data will be presented only for Part A, because Part B was cancelled, as mentioned earlier.

For safety summaries events that start from the first administration of any trial medication until 30 days (REP) after the last administration of any trial medication will be considered as having occurred “on-treatment”. If not specified otherwise, all safety tables will be based on the on-treatment period. Adverse events that have onset during the screening or the follow-up period will be displayed in separate listings from those that occurred during the on-treatment period. The MTD evaluation period will be defined as the period from 1st treatment administration (day 1) till day 21 inclusively.

Labels of each treatment period, the labels used for displays in the tables and listings in the CTR, as well codes, decodes, sort order and labels for each trial medication are provided in the TSAP technical documents.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Important protocol deviations will be summarised. The IQRMP specifies the important protocol deviations in detail. The following table specifies the different categories of IPDs.

Table 6.2: 1 Handling of iPDs

iPD code		iPD Category & Brief Description	Excluded from analysis set
A		**In/Exclusion criteria not met**	None
	A1	Inclusion criteria not met	None
	A2	Exclusion criteria not met	None
B		**Informed consent not available/not done**	
	B1	Informed consent not available/not done	All
	B2	Informed consent too late	None
C		**Trial medication and randomization violations**	
	C1	Incorrect trial medication taken	None
	C2	Administration not according to protocol	None
	C3	Administration of study medication which exceeded the limit of in-use stability	None
D		**Prohibited medication use**	
	D1	Concomitant medication	None
E		**Missing critical data**	
	E1	Missing of Vital signs (BP, PR, BT and SpO2)	None
	E2	Missing of 12-Lead ECG	None
	E3	Missing of Safety laboratory parameters	None
	E4	Important AE related data missing	None

6.3 SUBJECT SETS ANALYSED

The Screened Set (SCR) includes all patients who signed the informed consent form and will be used to summarise patient disposition.

The Enrolled Set (ES) includes all patients who have been enrolled into the study.

The Treated Set (TS) consists of all patients who have received at least one administration of trial medication and will be used for all planned safety, efficacy and biomarker analyses in the CTR besides the MTD determination.

The MTD Evaluation Set includes all patients who were documented to have received at least one dose of trial medication and were considered evaluable for MTD evaluation. This set will be used for the primary analyses of DLTs and MTD determination.

Rules for replacement of patients are defined in CTP Section 3.3.4.1. The list of replaced patients will be stored in the trial master file.

The Pharmacokinetic Parameter Set (PKS) consists of all patients in the TS who have at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability.

The ECG Set includes all patients in the treated set who do not have an artificial pacemaker and have at least one on-treatment value for at least one ECG variable.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable since there will be no inferential analyses. Thus, no statistical model in which centre or country is included as factor will be applied.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards (4). Missing data and outliers of PK data are also handled according to BI standards (5). PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed. Potential outliers will be reported and analysed as observed. In general, missing data not discussed in (4) and (5) will not be imputed unless required for the following analyses and definitions. Then the rules as described below apply.

1) **Change of laboratory values from baseline**

   Laboratory values at baseline: For missing laboratory data at cycle 1 day 1 (before the first administration of any study medication) the data of preceding visits will be used if available.

2) **Definition of on-treatment period and actual treatment**

   Date of permanent discontinuation of study medication: All reasonable efforts should be undertaken during the study to obtain the dates of permanent discontinuation of study medication. However, if the date of the very last administration is missing this will be imputed with:

   - If only month and year are given, the last day of the month will be used for imputation

- If only the year is given, the 31st of December of the given year will be used for imputation

If the imputed date leads to a date that is later than the date of the EOT visit, then the imputed date is the date of the EOT visit. If the imputed date leads to a date that is later than the death date, then the imputed date is the date of death.

3) ECG analysis

Quantitative and derived categorical ECG endpoints

- If single cardiac cycles are missing, the arithmetic means per single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.
- If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced (1 or 2) number of recordings.
- If the actual times of all triplicate pre-dose ECG recordings on Day 1 or the time of the first drug administration are missing, or the planned pre-dose ECGs are recorded after the first drug administration, they will not be used as baseline values and will be excluded from the analyses.
- If baseline is missing, a QTcF/QT interval > 500 msec at any time on treatment will be a notable finding.

Qualitative ECG findings

- In case a certain qualitative ECG finding is not reported at baseline but occurring on-treatment, this will be categorized as a 'new onset' of this finding.
- For the analysis of overall ECG interpretation values (comparison of on-treatment with baseline results), missing values will be handled as indicated in the following table.

Table 6.6: 1 Interpretation of qualitative ECG findings

Condition: Overall ECG interpretation		**Aggregated result presented in Table**
At baseline	**On treatment (specific time interval under consideration)**	**Overall ECG interpretation**
Normal, abnormal or missing/not evaluable	Normal (all time points)	Normal
Abnormal	Abnormal (at least one time point)	Abnormal, and abnormal at baseline
Normal or missing/not evaluable	Abnormal (at least one time point)	Abnormal (new onset)
Normal, abnormal or missing/ not evaluable	Missing/not evaluable (at least one time point), normal or missing/not evaluable at the other time points	Missing/not evaluable

Exposure-response analysis

- Missing BI 891065 plasma concentration data which are identified by "BLQ" in the comment field (below lower limit of quantification) will be replaced by ½ LLOQ (lower limit of quantification) if measured on-treatment.

4) Biomarker and pharmacodynamic analysis

Cytokines: For cytokines, we impute BLQ values with ½ LLOQ .

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the flowchart in the CTP.

Unless otherwise specified baseline is defined as the time point closest to but prior to the first administration of study medication. If no time is specified and the date is the same as the first administration date, then it will still be considered baseline if not specified otherwise. If there

is no measurement earlier than the first administration of study medication, then no baseline will be derived.

Laboratory values:
Baseline is defined as the latest time point before the very first administration of study medication. For laboratories where not only the examination date but also time are recorded, examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first administration of study medication is considered as baseline value only if the time of laboratory assessment is before or the same as the time of first study drug administration.

If any of these times is missing and the date of laboratory assessment is equal to the date of first administration of study medication, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

Imaging time windows:
In order to identify whether consecutive imaging time points are missing for a given patient, a nominal time point (6, 12, … weeks etc.) will be assigned to each and every image. This is achieved by creating windows for every radiological response assessment. These windows are defined in Table 6.7: 1.

Table 6.7: 1 Nominal time points and windows for imaging

Nominal time point (weeks from start of study medication)	**Planned date of scans (relative day*)**	**Window (days)**
6	43	1 to ≤ 64
12	85	65 to ≤ 106
18	127	107 to ≤ 148
24	169	149 to ≤ 200
33	232	201 to ≤ 263
42	295	264 to ≤ 326
51	358	327 to ≤ 389
Etc., 9 week interval	Etc.	Etc.

* the date of the first dose of study medication is Day 1

If a patient does not have an image in one of the windows described above, he/she will be said to have missed an assessment for that time point.

ECG analysis:
Baseline values will be derived from the 1−3 triplicate ECG recordings prior to the first drug administration on Day 1 (refer to Section 7.8.4).

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow the BI guideline (8).

All analyses are presented only for Part A, as Part B was cancelled.

For End-of-Text tables, the set of summary statistics is: N / Mean / standard deviation (StD) / Min / Median / Max.

For tables that are provided for endpoints with some extreme data median, quartiles and percentiles should be preferred to Mean, StD, Min and Max.

For time-to-event analysis tables the set of statistics is: number of patients [N(%)], number of patients with event [N(%)], <time to event> [months] followed by P25 (25^{th} percentile), median, P75 (75^{th} percentile) and number of patients censored [N(%)]. If not specified otherwise the duration as well as the time to event will be displayed in months.

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 (%) relative to the respective treatment group (unless otherwise specified all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values. The denominator of the main categories is defined by the number of patients in the used patient set. The main categories define the denominators of the subcategories. Subcategories should be intended and "[N(%)]" will be displayed only for the main category. If a table includes only categorical data, "[N(%)]" is to be displayed in the column header.

Sort order for general categorical variables: If categories correspond to the collected categories on the eCRF and the table shells do not explicitly specify the ordering, the "default ordering" defined by the eCRF is to be used in such cases. If categories are derived, the ordering as specified in the table shell document should be used; in general ordinal data (e.g. categorised continuous data) are to be displayed in ascending order.

Abbreviations (e.g. Wors.) should not be displayed without any explanations. They will be either spelled out in the table or explained in footnotes (whatever is more reasonable from the programming point of view).

If applicable, conversion from days to weeks, months and years will be as follows:

- Weeks = Days / 7
- Months = (Days * 12) / 365.25
- Years = Days / 365.25

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics are planned for demographic characteristics, disease history, prior therapies, medical history, alcohol and tobacco use, baseline eastern cooperative oncology group (ECOG) performance status, and baseline disease assessment.

7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics are planned for this section of the report. Concomitant diseases will be coded similarly as adverse events based on the most current Medical Dictionary for Regulatory Activities (MedDRA) version. Concomitant therapies (CTs) will be coded according to World Health Organization Drug Dictionary (WHO DD). CTs will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorise CTs by therapy type. In situations where a medical product may be used for more than one equally important indications, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level 3 categories will be counted more than once. Footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

Treatment compliance will be listed in the appendix of the CTR. In general, the amount of and time for which BI 891065 is taken will be interpreted in light of treatment exposure, efficacy, and safety. Refer to Section 5.4.2 and Section 7.7 for further details on exposure analysis.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

The primary endpoints of Part A are the MTD of BI 891065 and the number of patients with DLTs in the first treatment cycle. The number of patients with DLTs at each dose level will be presented for the first cycle for the MTD evaluation set and for the whole on-treatment period for the treated set separately.

The MTD will be determined by the SMC using recommendations from a Bayesian logistic regression model (BLRM, see CTP Section 7 for details on the model and on the prior). BLRM evaluations for the CTR will be performed once using the number of patients with DLTs during the first cycle from the MTD evaluation set and once using the number of patients with DLTs during the whole on-treatment period from the treated set.

Tables and bar charts displaying the posterior probabilities of the true DLT rates being in either the underdosing interval, the targeted toxicity interval or the over toxicity interval will be produced.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

Not applicable as no key secondary endpoints have been defined in the CTP.

7.5.1.1 Primary analysis of the key secondary endpoint(s)

NA

[redacted]

7.5.2 (Other) Secondary endpoint(s)

Part A:

PK endpoints will be analysed descriptively as well. Plasma (and urine) concentrations of BI 891065 will be plotted against time. The calculation of the PK parameters, as well as the descriptive and comparative analysis of the PK parameters, will be based on the methods outlined in Section 7.3.1.2 of the CTP, as well as in (9).

[redacted]

7.7 EXTENT OF EXPOSURE

For Part A, duration of BI 891065 intake will be summarised descriptively. The number of patients with at least one dose reduction of BI 891065 will be displayed descriptively, and the time to first dose reduction of BI 891065 will be analysed descriptively as well using Kaplan-Meier methods based on the treated set. Patients who discontinue BI 891065 without a dose reduction will be censored at the date of the last BI 891065 intake for this analysis. Furthermore, dose intensity of BI 891065 will be calculated.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS, besides the analyses of MTD determination. These will be performed on the MTD evaluation set.

7.8.1 Adverse Events

The analyses of AEs will be descriptive in nature. All analyses will be based on the number of patients with AEs (not on the number of AEs). The analysis will be based on BI standards (6). AEs will be coded using the most recent version of MedDRA. According to the BI standards multiple overlapping or adjacent recordings (AE occurrences) of the same AE are collapsed into one AE event if all AE attributes are identical (lower level term, severity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest (AESI) flag).

The analyses of AEs will be based on the concept of treatment-emergent AEs, where a treatment-emergent AE has an onset in the analysing treatment period. The AE analysis will be based on the on-treatment period which starts with the date of the first administration of study medication and ends 30 days after the last administration of study medication. AEs with an onset date in the screening period (time between informed consent date and date of the first administration of study medication) or follow-up period (time after the on-treatment period) will be tabulated and listed separately.

Sorting order: In AE tables, system organ classes (SOCs) will be sorted alphabetically and preferred terms (PTs, within SOCs) will be sorted by descending frequency.

Listings of AEs will be displayed by patient. The actual planned dose of BI 891065 will be derived and included in the listings. AEs will be reported with start day and end day as calculated from the first day of treatment with study medication. For listings displaying AEs during the screening or follow-up period, the start and stop day are calculated from the start of the respective analysis period.

The incidence of AEs overall, related AEs and serious AEs (SAEs) will be reported by severity according to common terminology criteria for adverse events (CTCAE) grades. Drug-related serious AEs will also be tabulated. Protocol-specified AESI will be analysed based on data reported in the eCRF.

AEs leading to death during the on-treatment period will be tabulated by SOC and PT. Reported fatal AEs during the follow-up period will be listed.

Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction of BI 891065 or permanent discontinuation of study medication. Their incidence will be reported by severity according to CTCAE grades. A listing of patients who developed other significant AEs will be provided and a flag for serious and non-serious will be included. In addition, AEs leading to treatment interruption will be reported by severity according to CTCAE grades.

7.8.2 Laboratory data

The analysis of laboratory data will be descriptive in nature and will be based on BI standards (7). The same on-treatment period as considered for the analysis of adverse events will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses. Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline values will be displayed in a new category "missing CTCAE grade at baseline" for those laboratory parameters where CTCAE grading is applicable. Descriptive statistics, including change from baseline and frequency of patients with transitions relative to the reference range, will be provided. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE v5.0.

For Primary laboratory tests listed in Table 7.8.2: 1, the following outputs will be presented:

- Descriptive statistics, including changes from baseline
- Shift tables in terms of:
    - CTCAE grade, for laboratory tests with CTCAE grade defined;
    - Upper and lower reference limits, for laboratory tests without CTCAE grades;
    - Multiples of upper reference limit for customized shift tables of ALP, ALT, AST, total bilirubin and creatinine.
- Frequency of patients with potential clinically significant abnormalities.

For secondary laboratory tests listed in Table 7.8.2: 2, analyses will be limited to frequency of patients with potential clinically significant abnormalities.

For other laboratory tests, only listing of observed values will be presented.

Analyse of descriptive statistics should use normalized lab values. Analyses of frequencies of patients with potential clinical significance, analyses of shift, and liver function categories tables should use converted values.

Table 7.8.2: 1 Primary laboratory tests

Table 7.8.2: 2 Secondary laboratory tests

Label	Lab test name	Direction of interest	Potential Clinical significance rule
ALB	Albumin	Low	A[1]
APTT	Activated Prothrombin Time	High	A[1,2]
CA	Calcium	Low, High	A[1]
CL	Chloride	Low, High	Low: <80 mmol/L and <baseline High: >120 mmol/L and >baseline No CTCAE defined
EOS	Eosinophils	High	>1.0*10^9/L and > baseline No CTCAE defined
GGT	Gamma Glutamyl transferase	High	CTCAE Grade 2 or higher
PHOS	Phosphate	Low, High	High: >1.7 mmol/L and >baseline Low: <0.7 mmol/L and <baseline No CTCAE defined
PROT	Serum Protein	High	>ULN and >baseline No CTCAE defined
PT	Prothrombin Time	High	>ULN and > baseline No CTCAE defined
URIC	Uric Acid	High	Females: >600 umol/L and >baseline Males: >650 umol/L and >baseline CTCAE based upon AE

[1]A= CTCAE grade 2 or greater with an increase of at least one CTCAE grade from baseline
[2]CTCAE grading will not consider symptoms presence of bleeding or use of anticoagulation.

Worst laboratory value and its CTCAE grade (highest CTCAE grade) over all courses will be calculated for each laboratory parameter.

The last laboratory value on treatment is the laboratory value of the last visit during the on-treatment period of each patient.

Laboratory values without CTCAE grading will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range at baseline, for the maximum value on treatment and for the last measurement on treatment.

Differential blood count:

Differential blood counts were to be measured in absolute values according to the CTP. In case a subject's differential blood count is reported in percentage, the following conversion will be applied:

Differential [10^9/L] = Differential [%] * (White blood cell count value / 100)

The corresponding reference ranges of the converted differential blood values are not allowed to be converted like the individual laboratory measurements. The reference range is taken from the BI standard reference range definition.

Urine analysis based on dipstick:
To ensure medically rational and consistent BI internal handling of urine laboratory values assessed by dipstick only, no analyses based on CTCAE grades will be done for urine. For urine measurement based on dipsticks the indicated results will be converted as described in Table 7.8.2: 3 for the analysis and displayed in the urine analysis tables.

Table 7.8.2: 3 Conversion of urine measurements based on dipsticks

Original dipstick measurement	Converted dipstick measurement
"-" ; "NEG" ; "NEGATIVE" ; "NORMAL"	0.0
"0.5" ; "TRACES" ; "TRACE" ; "+/-" ; "+-" ; "-/+"	0.5
"+" ; "1+"; "SMALL"	1.0
"++" ; "2+"; "MODERATE"	2.0
"+++" ; "3+"; "LARGE"	3.0
"++++" ; "4+"	4.0

Handling of CTCAE grade -1 and -9 laboratory parameters:
Generally, in case only one direction of worsening (high or low laboratory value) is specified in the CTCAE document, there is no need to examine the other direction. Therefore, for calculating the change in CTCAE grade, patients with a CTCAE grade of -9 (no CTCAE grade defined) will be automatically treated as CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade will be displayed as -9.

There are certain parameters for which CTCAE grades can only be attributed by taking physiological consequences into account. These laboratory values will be coded as -1. As these definitions aggregate laboratory data and adverse events or concomitant therapies no analyses based on CTCAE grades will be done. Instead standard laboratory analyses as for laboratory parameters without CTCAE grade definitions will be done. Nevertheless, a laboratory listing including -1 values will be added to the CTR.

Corrected calcium:
The grading of hypocalcemia is based on corrected calcium as calcium can be falsely low if hypoalbuminemia is present. The following corrective calculation will be performed:

Corrected calcium (mg/dL) = Total Calcium (mg/dL) – 0.8[Albumin (g/dL)-4]

No correction of the reference range has to be done. The reported reference range of total calcium will be used for analyses.

Corrected calcium can be only derived at a certain time points in case both laboratory values total calcium and albumin have been reported for the patient in the same laboratory sample.

Hepatic enzyme elevations (potential Hy's law cases):
These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of ALT and/or AST > 3ULN (upper limit of normal) with total bilirubin ≥ 2ULN. The events can occur in any order, but must occur within 14 days of the previous event, i.e. the second event must occur within 14 days of the first event, and the third event must occur within 14 days of the second event, etc. Patients with missing laboratory values for liver enzymes will be excluded from these analyses, but presented separately.

Tabulations of hepatic enzyme elevations and liver laboratory values will be done according to the FDA Drug Induced Liver Injury (DILI) guidance (10).

Hepatic enzyme elevations will be displayed for the treated set for the whole on-treatment period.

7.8.3 Vital signs

Descriptive statistics are planned for the analysis of vital signs.

7.8.4 ECG

For Part A, analyses of ECG will be descriptive in nature. Newly emergent abnormalities will be recorded and analysed as adverse events. CTCAE Version 5.0 will be used for those ECG variables.

In addition, statistical ECG analyses will be performed for the centrally evaluated digital ECG recordings as follows.

Derivation of ECG variables

Three replicate digital ECG recordings will be collected as specified in the flowchart of the CTP. Each of the three recorded single ECGs will then be evaluated semi-automatically for cardiac intervals, which comprise the RR, PR and QT interval and the QRS complex. Measurements of these intervals will be made on four (possibly consecutive) cardiac cycles from the lead chosen (usually lead II). The measurements of the cardiac cycles will be stored in the database, i.e. usually 12 values per time point. The four cardiac cycles will be averaged prior to the calculation of the heart rate and heart rate corrected QT intervals (QTc).

The heart rate will be derived from the RR interval as

$$HR\ [beats/min] = 60000/RR\ [msec]$$

Heart rate corrected QT intervals (generally denoted by QTc) will be calculated using Fridericia's (QTcF) formula and Bazett's formula (QTcB):

- QTcF [msec] = (1000/RR)^(1/3) * QT [msec]
- QTcB [msec] = (1000/RR)^(1/2) * QT [msec]

Further aggregation of the three replicate ECG intervals and HR at each scheduled time point will then be performed using arithmetic means. Additional averaging over 3 time points will be performed to derive the baseline values: they will be calculated as the mean values of the 3 triplicate ECG recordings collected pre-dose on Day 1.These mean values will be used for the derivation of the ECG variables as they are specified in Section 5.4.3.

ECG analyses

For all ECG variables, listings of individual data will be shown in the appendix of the CTR. Absolute values and changes from baseline in QTcB interval as well as the percentage changes for PR interval and QRS complex will only be displayed in listings.

Absolute values and changes from baseline in QTcF interval, QT interval, HR, PR interval, and QRS complex will be summarised descriptively by treatment, cycle, day, and time point using the ECG set. The time profiles of mean and standard deviation for the absolute values and changes from baseline on treatment will be displayed graphically by treatment.

Frequency tables will be provided for all categorical variables including notable findings and qualitative ECG findings. The tables will be presented separately for the visit days where an ECG profile has been taken as well as for the overall on-treatment period using the maximum value per patient. Frequencies of the increases in QTcF and QT intervals above thresholds as defined in Section 5.4.3 between baseline and on-treatment will be displayed in two-way shift tables by treatment. Frequency tables with regard to the new onset of qualitative (morphological) ECG findings will display categories of grouped findings based on the CDISC (EGTEST) terminology as well as the frequencies per each observed type of finding. These descriptive analyses will be performed for patients in the ECG Set for Part A.

For all patients with any notable finding (see Section 5.4.3), a separate listing in Section 15 of the CTR will be created and the corresponding time profiles will be shown. Notable findings of patients in the TS who are excluded from the ECG Set will be listed in separate listings.

Exposure-response analysis

All exposure-response analyses will be based on the ECGPCS. The decision whether plasma concentration values, which are excluded from the descriptive PK analyses, are to be excluded from the exposure-response analysis as well, is to be made no later than at the RPM before data base lock. Pairs of BI 891065 plasma concentrations and QTcF changes from baseline that are not time-matched (i.e. an unacceptable time deviation between PK blood sampling and ECG recording) will be excluded from the analysis. The maximum time deviation between PK blood sampling and ECG recording at different time points during the trial that will be accepted for the analysis are listed in Table 7.8.4: 1. For pre-dose pairs, both measurements had to be collected before the corresponding drug administration; for post-

dose pairs, both measurements had to be collected after the corresponding drug administration. In case the collecting time of the PK blood sample and/or the ECG recording is not available, the pair will also be excluded from the analysis.

Table 7.8.4: 1 Maximum acceptable time deviations between PK sample and ECG recording

Timepoint of ECG recording*	**Acceptable deviation**	**Timepoint of ECG recording***	**Acceptable deviation**
C1D1, -1:00, -0:30, -0 :15	NA	C1D15 predose	NA**
C1D1 1:00	+ 8 minutes	C1D15 1:00	+ 8 minutes
C1D1 2:00	+ 8 minutes	C1D15 2:00	+ 8 minutes
C1D1 3:00	+ 8 minutes	C1D15 3:00	+ 8 minutes
C1D1 24:00 (Part A)	NA**	C1D16 predose	NA**

*Time relative to BI 891065 administration

** No restrictions on the acceptable deviation are imposed in both directions. However, if the PK sample was taken before the ECG recording but the resting time in between was shorter than 10 minutes, the pair of measurements will be excluded.

Graphical representations:
The relationship between BI 891065 plasma concentrations and QTcF, HR and QT changes from baseline will be investigated graphically. To inspect whether the peaks of the time-profiles for BI 891065 plasma concentrations and QTcF interval changes from baseline (or HR/QT changes from baseline respectively) coincide, figures of the individual time profiles of BI 891065 plasma concentrations and QTcF will be generated for each patient.

For further visualization of the relationship, plasma concentration against QTcF changes from baseline (or HR/QT changes from baseline, respectively) will be plotted.

If deemed necessary, these analyses might also be performed in addition using the corresponding variables based on the PR interval and the QRS complex.

Appropriateness of QT interval correction methods

To evaluate the appropriateness of the methods, slopes of the relationship of QT, QTcF, and QTcB interval versus RR interval (log-transformed values) will be estimated by applying a random coefficient model. This analysis will be based on the three single on-treatment ECG recordings per time point. A table of the resulting (fixed effects) slopes will be displayed together with two-sided 95% confidence intervals in the appendix of the CTR. The model is defined as follows (11):

$$Y_{ik} = \mu_0 + s_{0i} + (\delta_1 + s_{1i})X_{ik} + e_{ik},$$

$$(s_{oi}, s_{1i}) \sim N_2\ (\mathbf{0}, \Sigma), e_{ik} \sim iid\ N(0, \sigma^2),$$

where i=1,...,I indicates the patient and k=1,…,K the number of the measurement,

Y_{ijk} is the log-transformed QT interval of measurement *k* in patient *i*,

μ_0 is the overall intercept,

s_{0i} is the random effect on intercept associated with patient *i*,

δ_1 is the common slope associated with the relationship between the log-transformed QT and RR intervals,

s_{1i} is the random effect on slope associated with patient *i*,

X_{ik} is the log-transformed RR interval of measurement *k* in patient *i*,

e_{ik} is the random error associated with the measurement *k* in patient *i*, and

Σ is a 2-by-2 unstructured covariance matrix.

The random effects s_{0i} and s_{1i} are assumed to be independent of the random errors e_{ik}.The analysis will be based on single ECG recordings that will be log-transformed using the natural logarithm.

7.8.5 Others

Pregnancy tests:
A listing showing the results of pregnancy tests will be provided.

Cytokine data:
Descriptive statistics for absolute values, absolute change from baseline and mean change from baseline by treatment will be provided.

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.	Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009 Jan; 45(2): 228-47 [R09-0262]
3.	Seymour L, Bogaerts J, Perone A, Ford R, Schwartz LH, Mandrekar S, et al. RECIST Working Group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017; 18(3): e148-e152 [R17-0923]
4.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
5.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
6.	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
7.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
8.	*001-MCP-090:* "BI Style Guide", current version; IDEA for CON.
9.	*001-MCS-36-472_RD-01:* "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
10.	Guidance for industry: drug-induces liver injury: premarketing clinical evaluation (July 2009). Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2009) [P09-12413]
11.	Ring A. Statistical models for heart rate correction of the QT interval. Stat Med 29, 786 - 796 (2010) [R10-2920]
12.	Hoffman D, Kringle R, Lockwood G, Turpault S, Yow E, Mathieu G. Nonlinear mixed effects modelling for estimation of steady state attainment. Pharm Stat. 2005. [R05-0788]

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**31-Jul-2020**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Final	**18-Mar-2021**		All	This is the final TSAP
Revised				

APPROVAL / SIGNATURE PAGE

Document Number: c33486288 **Technical Version Number:1.0**

Document Name: 8-01-tsap-core

Title: An open label, Phase I study of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist	[redacted]	19 Mar 2021 07:19 CET
Author-Trial Statistician		19 Mar 2021 07:34 CET
Approval-Clinical Trial Leader		19 Mar 2021 07:57 CET
Approval-Medical Writer		19 Mar 2021 08:32 CET
Approval-Team Member Medicine		19 Mar 2021 09:04 CET
Approval-Project Statistician		19 Mar 2021 10:22 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed