TRIAL STATISTICAL ANALYSIS PLAN

c10164918-03

BI Trial No.:	1315.2
Title:	An open-label, Phase I/II trial to determine the maximum tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 836858 in combination with decitabine in patients with acute myeloid leukemia Including: Protocol Amendment 1 [c03377067-02] Protocol Amendment 2 [c03377067-03] Protocol Amendment 3 [c03377067-04] Protocol Amendment 4 [c03377067-05] Protocol Amendment 5 [c03377067-06] Protocol Amendment 6 [c03377067-07]
Investigational Product(s):	BI 836858
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	19NOV 2019 SIGNED
Version:	Final

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[redacted]

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LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse events of special interest
ALKP	Alkaline phosphatase
ALT	Alkaline aminotransferase
AST	Aspartate aminotransferase
ATC classification	Anatomical, Therapeutic, Chemical classification
AUC	Area Under Curve
BI	Boehringer Ingelheim
BLRM	Bayesian logistic regression model
BSA	Body Surface Area
RPM	Report planning meeting
C_{max}	Maximum measured plasma concentration of the analyte
CL	Total plasma clearance
CR	Complete Remission
CRi	Complete Remission with incomplete marrow recovery
CT	Concomitant therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Data Base Lock
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DMS	Data Management and Statistics
DOR	Duration of Remission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDISH	Evaluation of Drug Induced Serious Hepatotoxicity
EFS	Event free survival
eCRF	Electronic case report form
ICH	International Conference on Harmonisation

Term	Definition / description
iPD	Important Protocol Deviation
IRR	Infusion Related Reaction
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical and Quality Review Meeting
MTD	Maximum tolerated dose
NE	Not evaluable
OR	Objective response
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
PKS	Pharmacokinetic set
PR	Partial remission
PT	Preferred term
PV	Protocol deviation
REP	Residual effect period
REPd	Duration of residual effect period in days
RFS	Relapse free survival
RP2D	Recommended phase 2 dose
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
SS	Screened set
TCM	Trial Clinical Monitor
TF	Treatment failure
t_{max}	Time from dosing to the maximum plasma concentration of the analyte
TOC	Table of contents
TS	Treated set

Term	Definition / description
TTF	Time to treatment failure

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 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. This TSAP follows the Boehringer Ingelheim (BI) internal reference (2).

This TSAP is based on the Project SAP wherever possible. Wordings like "randomisation (first administration of study treatment in non-randomised trials)" should therefore be interpreted as applicable.

Furthermore, in this combination trial the term investigational medicinal product is used for BI 836858 while combination drug denotes the backbone chemotherapy decitabine. The term trial medication is used for any of the two trial drugs.

SAS Version 9.4 or later version will be used for all analyses.

Due to company decision to stop this project, there is no Phase II subject enrollment so that Phase II analyses stated in CTP will be omitted.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Due to the decision to discontinue the development of BI865868, the enrollment was stopped after Phase I extension and Phase II part of the trial was cancelled as stated in CTP amendment 7.0. Thus there will be no data collection nor analyses for Phase II part .

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Phase I

The primary endpoints in the Phase I part of the trial are the maximum tolerated dose (MTD) and the number of subjects with of dose limiting toxicity (DLT) during the MTD evaluation period.

Maximum tolerated dose (MTD):

The MTD is defined as the highest dose of BI 836858 (in combination with decitabine) with less than 25% risk of the true DLT rate being above 33% during the MTD evaluation period.

MTD evaluation period:

The MTD evaluation period is defined as the time from the first administration of study drug to the start of the second treatment cycle or the end of 30-day residual effect period after last administration of study drug, whichever comes first. Subjects who were replaced during the MTD evaluation period will not be considered for MTD determination. The subjects who are completed the MTD evaluation period without being replaced are considered MTD evaluable.

In case a subject has not completed the required number of administrations due to BI 836858 related toxicity, he/she will not be replaced and this will be considered as DLT. However, subjects who have not completed the required number of administrations of BI 836858 for reasons other than BI 836858 related toxicity will be replaced. Subjects who were replaced during the MTD evaluation period will not be considered for MTD

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

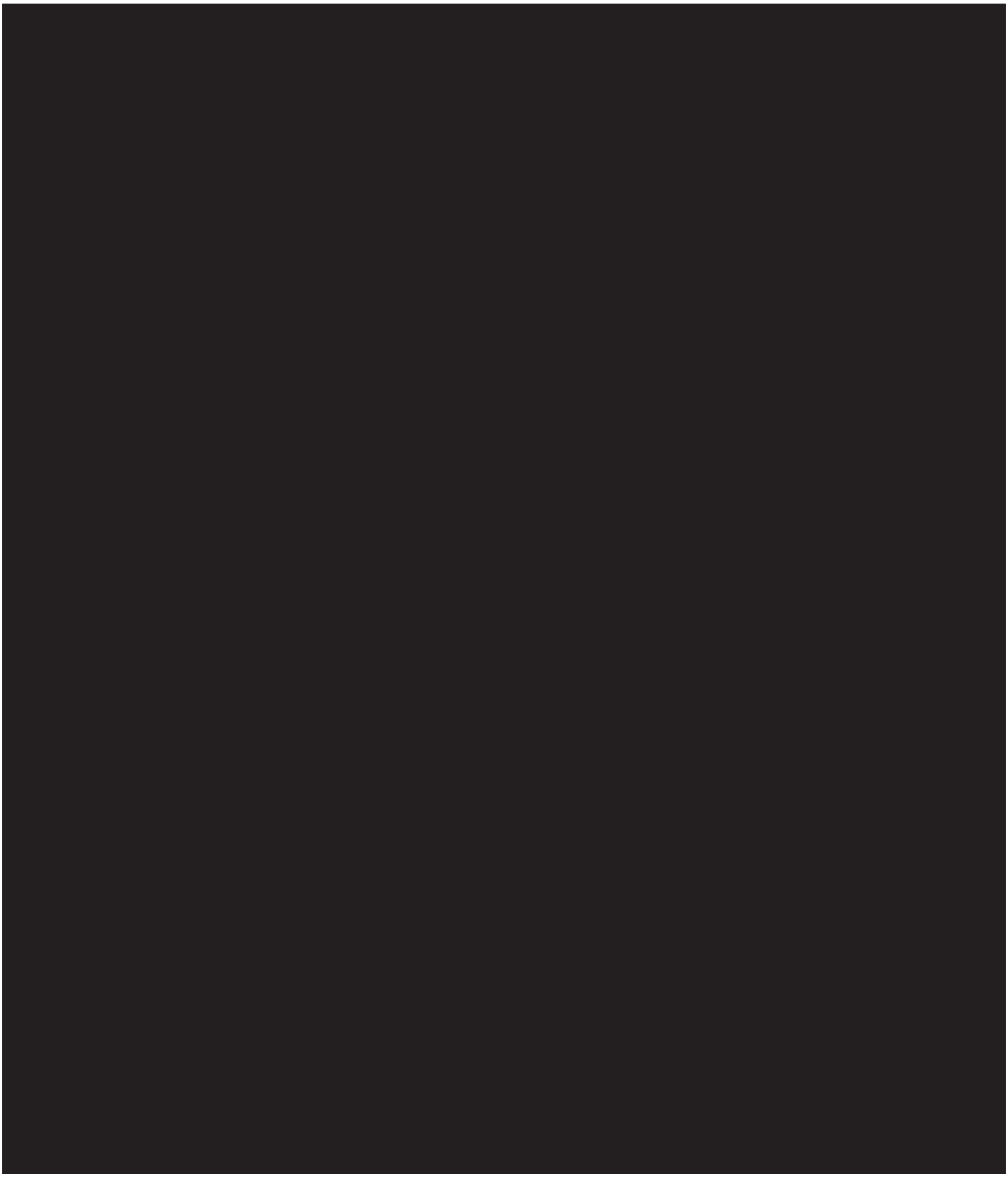
No key secondary endpoints are defined in this study.

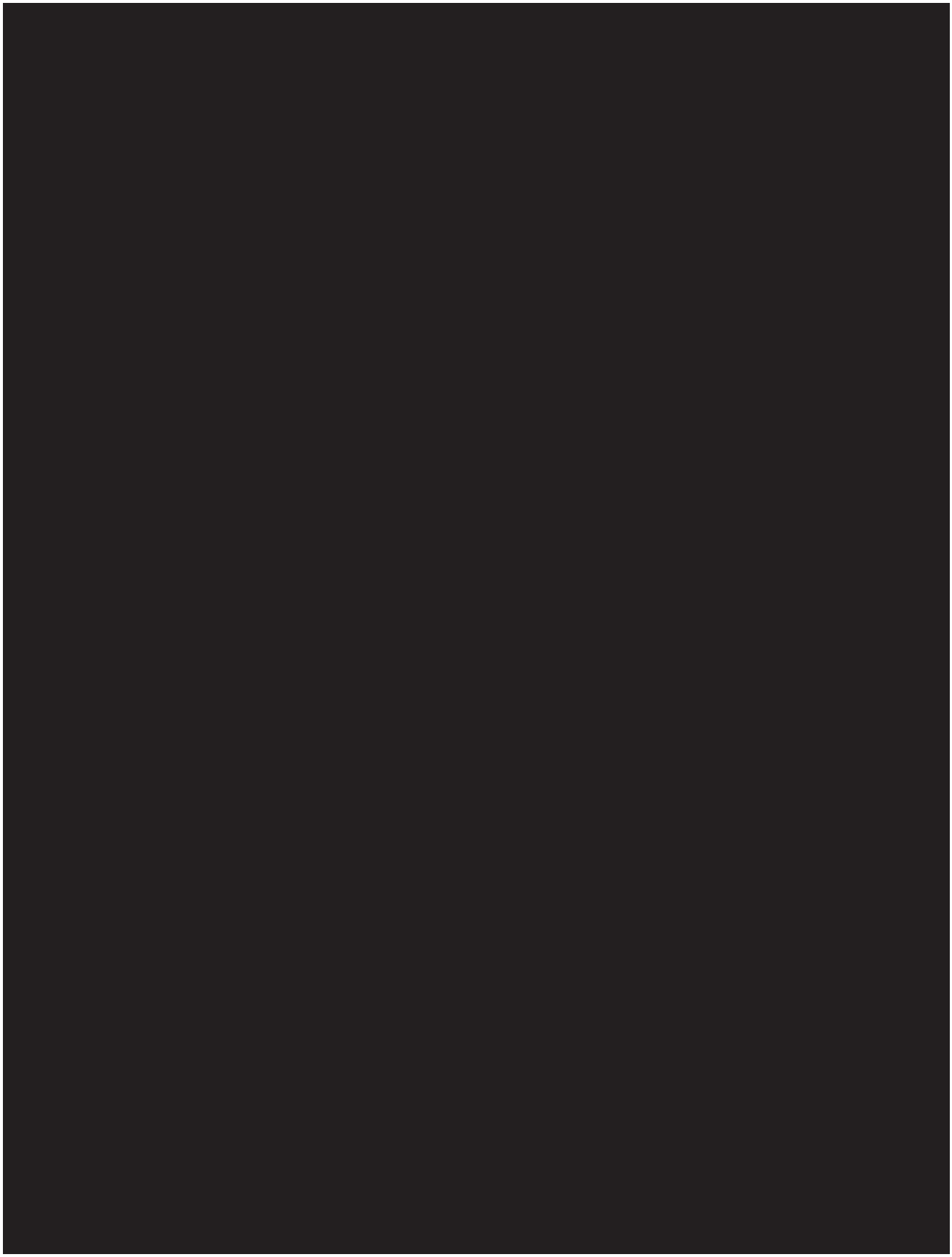
5.2.2 Secondary endpoint(s)

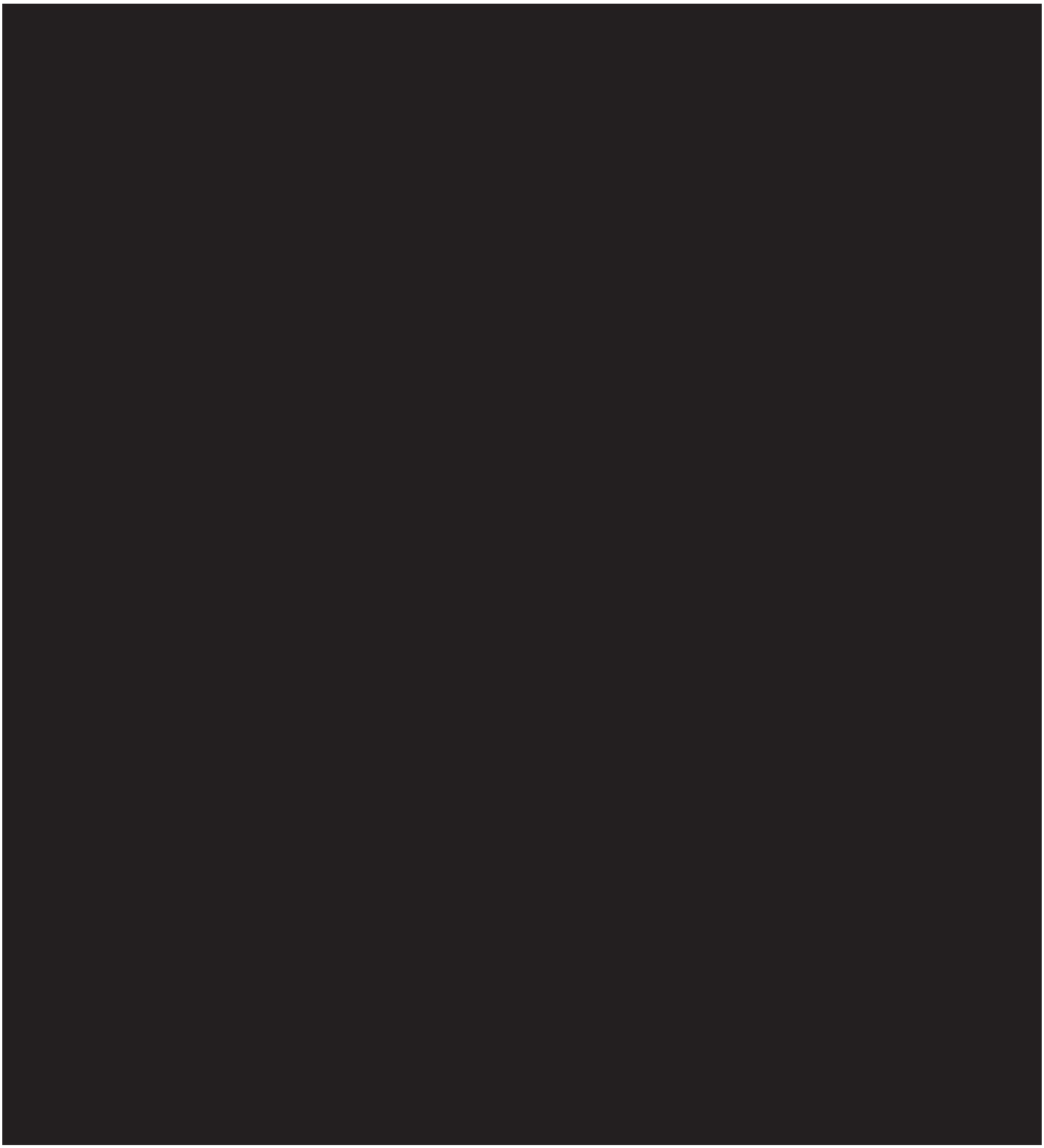
Phase I

- Number of subjects with objective response combining
  - Complete remission (CR)
  - CR with incomplete blood count recovery (CRi)

- Time frame: From start of treatment until the earliest of progression, death or end of trial (approximately up to 30 months).







6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Phase I

In the Phase I Part, treatments are not randomized (open-label, dose escalation). Different dose levels of the investigational medicinal product (BI 836858) can arise while combined with fixed dose of decitabine at 20 mg/m² per day. The data will be presented for all dose cohorts separately, in particular, subjects will be analysed by the dose cohort initially assigned in the first treatment course.

Table 6.1:1 Definition of analysing treatment periods

Analysing treatment period	**Start date (including)**	**Stop date (excluding)**
Screening	Date of informed consent	Date of first administration of trial medication
MTD evaluation period	Date of first administration of trial medication	First of start of the second treatment cycle or the end of the 30-day residual effect period
On-treatment	Date of first administration of trial medication	Start date of 'Follow-up'
Follow-up	Date of end of REP +1	Start date of 'Post-study'
Post-study	Last date subject status obtained / last date subject known to be alive + 1 (if subject is lost to follow-up) / date of refusal + 1 day / the date subject died + 1	During the trial: open / empty; after database lock (DBL): DBL + 1 day

Data recorded between the first administration of trial medication until up to 30 days (Residual effect period; REP) after the last administration of trial medication will be considered as on-treatment.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Even though no per protocol population is defined, subjects with potentially important protocol deviations (iPD) will be identified and documented. Potentially important protocol deviations are defined in Table 6.2:1. The final list of iPDs will be confirmed at the last report planning meeting (RPM) before the database lock at the time of the CTR.

If any manual iPDs are identified, they are to be summarized into categories and will be captured in the MQRM/RPM minutes via an accompanying Excel spreadsheet (3).

Table 6.2:1 Important protocol deviations

Category/ Code		Description	Comment/Example	Excluded from
A		**Inclusion/Exclusion Criteria**		
	A1	**Criteria related to safety**		
	A1.1	Patient has condition that may cause additional risk from study medication	EX 7, EX 12, EX 19	None
	A1.2	Patient has laboratory assessments that may cause additional risk.	EX 8-11	None
	A1.3	Patient is unable to comply with the protocol	EX 13, EX 20	None
	A2	**Criteria related to efficacy**		
	A2.1	Patient does not have trial diagnosis or is not part of the target population	IN 1-4, EX 1, EX 2	None
B		**Legal criteria**		
	B1	Informed consent not available/not done	IN 5	All
	B2	Informed consent after visit 1	IN 5	None
	B3	Men or women who are sexually active and not using adequate contraception.	EX 16, EX 17	None
	B4	Pregnant or nursing female patient	EX 15	None
	B5	Patient's age < 18	IN 1	None
C		**Administration of trial medication not in accordance with the protocol**		
	C1	Administration of trial medication not in accordance with the protocol	As marked in the eCRF, review and decision at medical and quality review meetings (MQRM) / report planning meetings (RPM)	None

Table 6.2:1 Important protocol deviations (cont.)

Category/ Code		Description	Comment/Example	Excluded from
	C2	Continuation of treatment although criteria for re-treatment are not met	Create listing, decision at medical and quality review meetings (MQRM) / report planning meetings (RPM)	None
	C3	Unjustified intra-patient dose-escalation	Create listing, decision at MQRM / RPM	None
	C4	Withdrawal of patient not performed according to CTP	Create listing, decision at MQRM / RPM	None
	C5	Discontinuation of decitabine not performed according to CTP	Create listing, decision at MQRM / RPM	None
	C6	Discontinuation of BI 836858 not performed according to CTP	Create listing, decision at MQRM / RPM	None
D		**Restrictions**		
	D1	Additional experimental anti-cancer, chemo-, immuno-, hormone - or radiotherapy during the study or too shortly before the study.	Create listing, decision at MQRM / RPM (and EX 6)	None
E		**Missing data**		
	E1	Baseline bone marrow assessment not within 14 days prior to first treatment	Create listing, decision at MQRM / RPM	None
	E2	Missing disease assessment at a time point where disease assessment was required	Create listing, decision at MQRM / RPM	None

6.3 SUBJECT SETS ANALYSED

Where applicable, the following subject sets will be defined for the Phase I and Phase II part separately.

- Screened set (SS): This subject set includes all subjects who have signed the informed consent. The SS will be used for subject disposition tables.
- Treated set (TS): This subject set includes all subjects who were documented to have received at least one dose of trial medication.
- MTD evaluable set: This subject set includes all subjects who were entered, treated and completed first cycle of planned treatment or subjects received at least 2 doses of BI 836858 due to BI 836858-related toxicity but not replaced.

[redacted]

[redacted]

[redacted]

6.5 POOLING OF CENTRES

Not applicable because centre/country is not included in the statistical

6.6 HANDLING OF MISSING DATA AND OUTLIERS

If not stated otherwise, missing data will not be imputed and remain missing. Potential outliers will be reported and analysed as observed.

Missing or incomplete AE dates are imputed according to BI standards (4).

[redacted]

For missing laboratory data at Visit 1 (before the very first administration of study medication) data from preceding visits will be used.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the CTP's flow chart.

Unless otherwise specified, baseline is defined as the time-point closest to but prior to first administration of trial medication in course 1. Note that for some trial procedures (for example body weight, vital signs, laboratory tests) this may be the value measured on the same day trial medication was started. In these cases it will be assumed that the

measurements were taken according to protocol, i.e. prior to first intake of any trial medication.

Laboratory values: Baseline is defined as the latest time-point before the very first administration of any trial medication in course 1. 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 trial drug administration is considered as baseline value if and only if the time of laboratory value is before or the same as the time of first trial drug administration.

7. PLANNED ANALYSIS

The labelling and display format of statistical parameters will follow the guideline "Reporting of Clinical Trials and Project Summaries" (7).

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard deviation (SD) / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles will be preferred to mean, standard deviation, minimum and maximum.

In general, means, medians, SD and percentiles will be presented to one more decimal place than the raw data Minima and maxima will be presented to the same number of decimal places as the raw data.

Tabulations of frequencies for categorical data will include all possible categories (even if with no count and also the missing category if there is missing data) and will display the number of observations in a category as well as the percentage (%) relative to the number of subjects in the respective treatment group (unless otherwise specified, all subjects in the respective subject 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.

If a table presents only categorical data, "N (%)" will be displayed in the column header only.

Abbreviations (e.g., Wors.) or acronyms (e.g., PD) will not be displayed in tables and Subject Data Listings (SDLs) without any explanation. They will be either spelled out or explained in footnotes.

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

- Weeks = days ÷ 7
- Months = 12 × days ÷ 365.25
- Years = days ÷ 365.25

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Standard descriptive analyses and summary tables are planned for this section of the report. Data will be summarized by treatment group and a "total" column will be included in the summary tables.

Body Surface Area (BSA):

$BSA[m^2] = 0.007184 \times height[cm]^{0.725} \times weight[kg]^{0.425}$

Time from first diagnosis [months] = (date of informed consent - date of first diagnosis +1)[days]×12/365.25

7.2 CONCOMITANT DISEASES AND MEDICATION

Only 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 WHO DD. CTs will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorize CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, subjects receiving CTs with more than one possible ATC level-three category will be counted more than once; footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report.

7.4 PRIMARY ENDPOINT(S)

Phase I

The primary endpoints are the MTD and the occurrence of DLT. The MTD is determined from the number of non-replaced subjects with DLT during the MTD evaluation period.

The MTD evaluation period is defined as the time from the first administration of study treatment to the start of the second treatment cycle or the end of the 30-day residual effect period after the last drug administration, whichever comes first. Subjects who were replaced during the MTD evaluation period are not considered for MTD determination. Those subjects who have completed the MTD evaluation period without having been replaced are referred to as subjects evaluable for MTD.

An overall summary of subjects with DLT(s) which occurred during the MTD evaluation period and the on-treatment period will be provided for each dose cohort.

Subjects who were treated but replaced are not considered for the MTD determination.

However, all information, including adverse events qualifying for a DLT from later times, will be considered in the final determination of the recommended Phase II dose (RP2D).

In order to describe the occurred dose escalation steps, a listing of all treated subjects will be provided. This will include the initial dose of the investigational medicinal product, subject number, treatment start date, DLT in MTD evaluation period [y/n], Evaluable for MTD [y/n] and will be sorted by treatment start date.

7.5 SECONDARY ENDPOINT(S)

Phase I

The secondary endpoint overall response will be listed only. If considered useful, aggregated tables will be provided where different doses might be grouped.

[redacted]

7.7 EXTENT OF EXPOSURE

Standard descriptive analyses over all treatment courses will be performed. This will include a summary of the variables defined in Section 5.4.1 and will comprise a mixture of frequency and percentages, as well as summary statistics.

The time to treatment discontinuation is defined as (date of last administration of trial medication– date of randomisation + 1). Subjects who have not discontinued treatment will be censored at the earliest of the following: date of last administration of trial medication, or date of data cut-off. Subjects who are randomised, but did never receive study medication will be censored on the day of randomisation

A Kaplan-Meier plot of time to treatment discontinuation by treatment group will be presented.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse Events

The analyses of adverse events (AEs) will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT the number of AEs.

The analyses will be based on BI standards. Adverse events will be coded with the most recent version of MedDRA. The severity of AEs will be scaled according to CTCAE version 4.03.

Reporting will be done according to version 6 of the AE guideline (8).

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences.
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence.

For each subject, all episodes with the same preferred term (PT) (system organ class, SOC) will be counted only once using a worst case approach for all AE attributes including CTCAE grading.

The analysis of adverse events will be based on the concept of treatment emergent adverse events, where a treatment emergent AE has an onset in the analysing treatment period. All adverse events occurring before first intake of trial medication will be assigned to 'screening' and all adverse events occurring after last intake of trial medication + 30 days will be assigned to 'post-treatment' (in randomized trials for listings only). For details on the treatment definition, see Section 6.1. In addition, a listing will be provided, detailing the actual treatment on the day when the adverse event started.

Adverse events of special interest (AESIs):

Adverse events of special interest (AESIs) are defined in CTP Section 5.3.8.1 as infusion related reactions (IRRs) of CTCAE grade >= 3, DLTs (occurring during the MTD evaluation period or repeated treatment courses), tumor lysis syndrome and drug induced liver injury (DILI).

Other significant AEs:

Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction or permanent discontinuation of study medication. Their incidence will be reported by severity according to CTCAE grades.

An overall summary of adverse events will be presented. This will include the number of subjects with AEs by worst CTCAE grade. The frequency of subjects with adverse events will be summarized by treatment, primary system organ class and preferred term. The system organ classes will be sorted by default alphabetically; preferred terms will be sorted by frequency (within system organ class).

AEs leading to dose reduction, AEs leading to overall permanent discontinuation, DLTs and Adverse events of special interest (AESIs) including Infusion Related Reactions (IRRs) will be tabulated.

Infusion related reactions (IRRs):

IRRs will be the object of special attention.

Subjects with any IRR will be tabulated by treatment and worst CTCAE grade. In addition, the number of infusions and the number of IRRs will be displayed by treatment.

The duration of IRR [h] and the time since start of the respective infusion [min] together with IRR related symptoms will be tabulated by infusion number and overall.

- Duration of IRR [h] = (End time of IRR - Start time of IRR) [seconds] / 3600
- Time since start of the respective infusion [min] = (Start time of IRR - Start time of infusion) [seconds] / 60

The relationship between the occurrence of IRRs and infusion rate as well as the administration of premedication will be examined.

For IRR summary, time since administration of treatment, duration of IRR, and related symptoms will be summarized descriptively by infusion timepoints.

User-defined AE categories (UDAEC)

User-defined AE categories (UDAEC) are defined in in Table 7.8.1:1. For UDAECs which contain sub-searches and/or two sensitivity levels (broad and narrow) all possibilities will be displayed on the UDAEC level in tables . For example for UDAEC “Infusion related infections” the tables will include the UDAEC “Infusion related reactions broad” and “Infusion related reactions narrow”. Similarly for UDAEC “Bleeding”, it will include “Bleeding - SMQ Haemorrhage”, “Bleeding - SMQ Haemorrhage laboratory terms broad”, “Bleeding - SMQ Haemorrhage laboratory terms narrow”, “Bleeding - SMQ Haemorrhage terms (excl. laboratory terms) narrow”.

Table 7.8.1:1 Definition of user-defined AE categories

Special Search Category	**Definition**	**Sensitivity**
Infusion related reactions (hypersensitivity)	SMQ 20000021 + infusion related reaction PT 10051792	Narrow (Algorithm)
Bleeding	SMQ Haemorrhage 20000038 SMQ Haemorrhage terms (excl. laboratory terms) 20000039	Narrow & broad Narrow
	SMQ Haemorrhage laboratory terms 20000040	Narrow & broad
Nausea	BIcMQ Nausea 30000078	Narrow & broad
Vomiting	BIcMQ Vomiting 30000091	Narrow & broad

Table 7.8.1:1 Definition of user-defined AE categories (cont.)

Special Search Category	**Definition**	**Sensitivity**
Drug related hepatic disorders	SMQ Drug related hepatic disorders 20000006	Narrow & broad
	SMQ Cholestasis and jaundice of hepatic origin 20000009	Narrow & broad
	SMQ Drug related hepatic disorders - severe events only 20000007	Narrow & broad
	SMQ Liver related investigations, signs and symptoms 20000008	Narrow & broad
	SMQ Liver-related coagulation and bleeding disturbances 20000015	Narrow & broad
ALT	BIcMQ Elevated Specific Liver Function Parameters sub-search1 30000022	Narrow & broad
AST	BIcMQ Elevated Specific Liver Function Parameters sub-search2 30000023	Narrow & broad
ALKP	BIcMQ Elevated Specific Liver Function Parameters sub-search3 30000024	Narrow & broad
gGT	BIcMQ Elevated Specific Liver Function Parameters sub-search4 30000025	Narrow & broad
Bilirubin	BIcMQ Elevated Specific Liver Function Parameters sub-search5 30000026	Narrow & broad
Neutropenia	BIcMQ Neutropenia 30000031	Narrow & broad
Cardiac disorders[1]	SMQ Ischaemic heart disease 20000043	Narrow & broad
	SMQ Cardiac failure 20000004	Narrow & broad
	SMQ Cardiac arrhythmias 20000049	Narrow & broad
Tumour Lysis Syndrome	SMQ Tumour Lysis Syndrome 20000219	All broad
	SMQ Torsade de point/QT prolongation Broad (20000001)	
	SMQ Cardiac arrhythmia terms broad (incl bradyarrhythmias and tachyarrhythmias) (20000050)	
	SMQ Convulsions broad (20000079)	
Fluid accumulation	HLT Total fluid volume increased 10044085	
	HLT Oedema NEC 10030113	

Table 7.8.1:1 Definition of user-defined AE categories (cont.)

Special Search Category	Definition	Sensitivity
	HLT Pulmonary oedemas 10037424	
	HLT Pneumothorax and pleural effusions	
	NEC 10035761	
	PT Ascites 10003445	
	PT Abnormal weight gain 10000188	
Infections	Infections (incl. respiratory infections and sepsis) - SOC 10021881 use label "Infections and infestations"	
	Infections (incl. respiratory infections and sepsis) - HLGT 10024970 use label "Respiratory tract infections"	
	Infections (incl. respiratory infections and sepsis) - HLT 10040054 use label "Sepsis, bacteraemia, viraemia and fungaemia NEC"	
Inflamed gut	PT Enterocolitis 10014893	
	PT Enterocolitis bacterial 10065206	
	PT Enterocolitis fungal 10065205	
	PT Enterocolitis helminthic 10065204	
	PT Enterocolitis infectious 10058838	
	PT Enterocolitis viral 10061841	
	PT Colitis 10009887	
	PT Enteritis 10014866	
Acute febrile neutrophilic dermatosis	PT Acute febrile neutrophilic dermatosis 10000748	

[1] A BIcMQ has been requested, however, as long as this is not available the terms as defined in Table 7.8.1:2 will be used.

Table 7.8.1:2 User-defined (sub-) search category of “Cardiac Failure”

Selected PTs for Cardiac Failure
Cardiac asthma
Cardiac failure

Table 7.8.1:2 User-defined (sub-) search category of "Cardiac Failure" (cont.)

Selected PTs for Cardiac Failure
Cardiac failure acute
Cardiac failure chronic
Cardiac failure congestive
Cardiac failure high output
Cardiac index decreased
Cardiac output decreased
Cardiogenic shock
Cardiomegaly
Cardiothoracic ratio increased
Dilatation ventricular
Left ventricular failure
Low cardiac output syndrome
Right ventricular failure
Oedema due to cardiac disease
Left ventricular dysfunction
Ejection fraction decreased
Cardiopulmonary failure
Diastolic dysfunction
Cardiac ventriculogram right abnormal
Cardiac ventriculogram abnormal
Cardiac ventriculogram left abnormal
Cardiac cirrhosis
Right ventricular dysfunction
Ventricular dysfunction
Cardiac resynchronisation therapy
Ventricular failure
Acute left ventricular failure
Acute right ventricular failure
Chronic left ventricular failure
Chronic right ventricular failure
Myocardial depression
Ventricular dyssynchrony
Systolic dysfunction
Neonatal cardiac failure

UDAEC will by summarized by dose cohort, search categories and preferred terms, and CTCAE grade. Some events contribute to more than one UDAEC. Patients with such AEs are counted in each of the UDAEC but are counted only once in the overall number of patients with an AE in any UDAEC.

Tumor Lysis Syndrome

In patients with a high tumor burden who are exposed to a highly effective therapy, there is a risk of rapid tumor destruction resulting in Tumor Lysis Syndrome (TLS).

Patients will be identified as having potential Tumor Lysis Syndrome if they met ***both*** of the following two criteria:

(1) Two or more of the laboratory parameters meet the criteria in Table 7.8.1:3,

a. time window

i. on the day of BI 836858 infusion or the following 6 days,

ii. at least two of the qualifying lab values must have occurred with the same 24 hour period

(2) Have an adverse event identified by the any of the SMQ in Table 7.8.1:4 or have a qualifying creatinine value

a. Time windows: AE onset or creatinine observation at any time during the treatment or residual effect periods

Table 7.8.1:3 Laboratory Signs of Cell Destruction

Laboratory parameter	**Abnormal value**
Uric acid	≥476 µmol/L AND increase from relative baseline[1] by ≥25%
Potassium	value ≥ 6.0 mmol/L AND relative baseline < 6.0 mmol/L
Inorganic phosphate	≥1.45 mmol/L AND increase from relative baseline by ≥25%
Calcium	<7 mg/dL[2] AND decrease from relative baseline by ≥25%

[1]Relative baseline is derived separately for each BI 836858 infusion as the last value prior to that BI 836858 infusion. Relative baseline will be derived independently for the four parameters, ie. four baseline values do not necessarily have to be derived from the same laboratory assessment.
[2]For calcium, 0.25* mg/dL= mmol/L

Table 7.8.1:4 Clinical Signs of Cell Destruction

Criterion
TLS broad SMQ [20000219]

Table 7.8.1:4 Clinical Signs of Cell Destruction (cont.)

Criterion
Torsade de point/QT prolongation broad SMQ [20000001]
Cardiac arrhythmia terms broad SMQ (incl bradyarrhythmias and tachyarrhythmias) [20000050]
Convulsions broad SMQ [20000079]
Creatinine Absolute increase from relative baseline by 26.5 µmol/L AND increase from relative baseline by ≥50%

For AEs during the post-treatment period, only subjects with drug related serious adverse event and protocol-specified AEs of special interest by treatment will be presented in listing.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (9). It will include a graphical summary highlighting potential cases of Hy's Law.

The analysis of laboratory data will use the same 'analysing treatments' as described for the AEs, except for that the baseline laboratory value will be included in the 'on-treatment period'. Subjects having at least one post-baseline laboratory value will be displayed in the descriptive analyses. The following parameters are of particular interest:

- haematology: haemoglobin, white blood cell count, Absolute Neutrophil Counts, platelets
- Biochemistry: aspartate transferase, alanine transferase, bilirubin, serum creatinine, urea, sodium, potassium, magnesium
- Coagulation: international normalised ratio, partial thromboplastin time

Laboratory values: Baseline is defined as the latest time-point before the very first administration of study medication. A laboratory value on the same date as the first study drug administration is considered as according to protocol, i.e. as prior to first study drug administration and will therefore be used as baseline value.

The following outputs will be presented:

- Worst CTCAE grade experienced during the on-treatment phase.

- Transitions of CTCAE grade from baseline to worst laboratory value, from worst to last laboratory value on treatment and from baseline to last laboratory value during the on-treatment phase.

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

The last laboratory value on treatment is the laboratory value of the last visit of the last course of each subject.

Furthermore, a summary table of possible clinically significant abnormalities will be given.

Possible clinically significant abnormal laboratory values are defined as those laboratory values that are of CTCAE grade ≥ 2 and show an increase from baseline value by at least one CTCAE grade. Frequency of subjects with possible clinically significant abnormal laboratory values will be provided whenever applicable. If no baseline value is available but the subject has a post-baseline laboratory value of CTCAE grade ≥ 2 an increase from baseline will be assumed, i.e. the laboratory value considered as possible clinically significant.

Hepatic injury:
As defined in the CTP a hepatic injury (DILI) is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT >3 fold ULN combined with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

Potential 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 with total bilirubin ≥ 2ULN and ALKP < 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. Subjects with missing laboratory values for liver enzymes will be excluded from these analyses.

In addition, eDISH plot will be by plotted to display the maximum on-treatment AST/ALT and maximum bilirubin in terms of ULN.

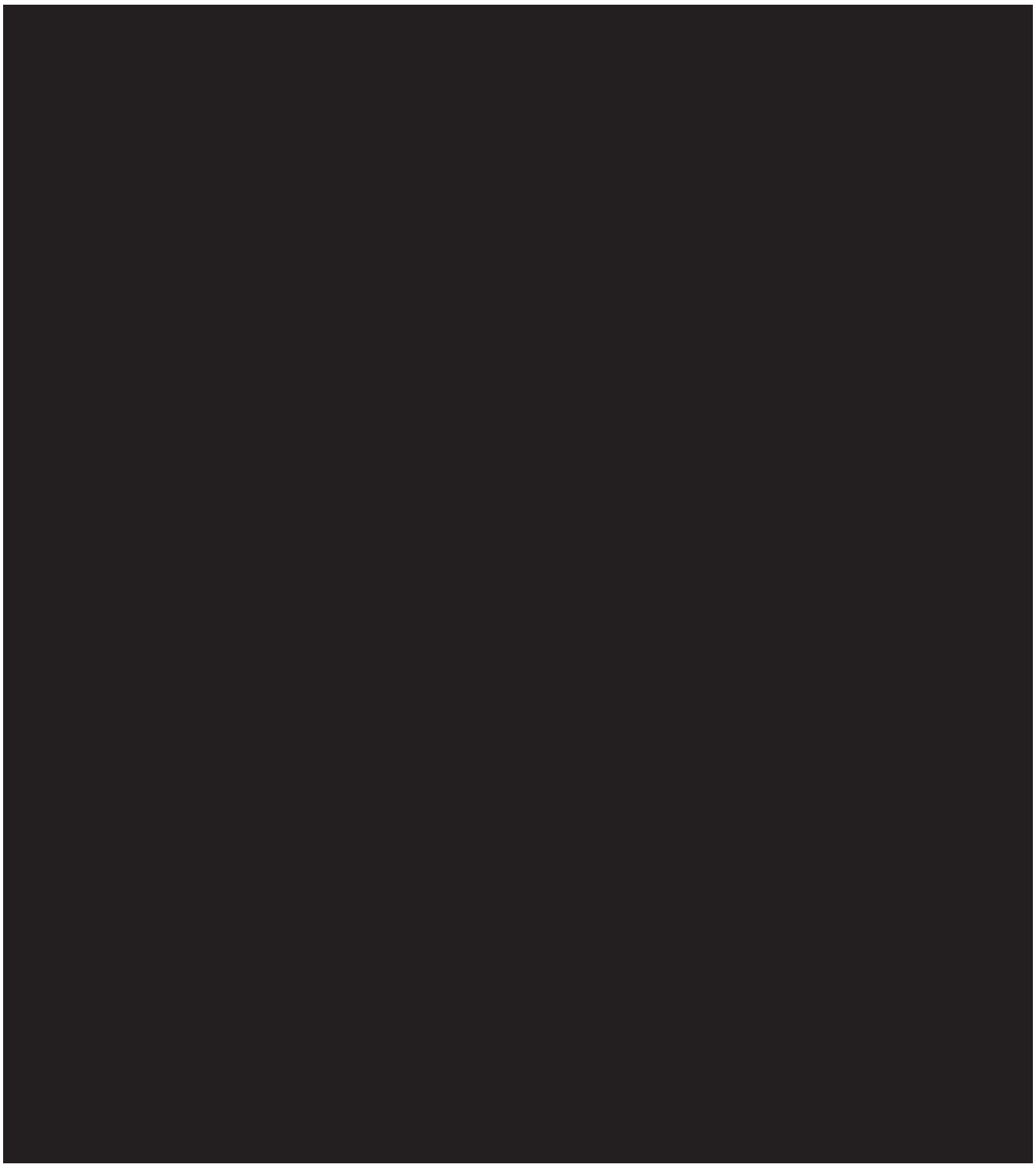
Neutrophil and platelet counts of each patients will be plotted in log scale graphs.

7.8.3 Vital signs

Only descriptive statistics are planned for vital sign report. Observed value and change from baseline values will be summarized.

7.8.4 ECG

12-lead resting ECGs are done throughout the study and are assessed for pathological results which are to be recorded as either concomitant disease or AE by the Investigator. ECG results will be listed.



8. REFERENCES

1	*CPMP/ICH/363/96* : "Statistical Principal for Clinical Trials", ICH Guideline Topic E9 Step 5; Note For Guidance on Statistical Principal for Clinical Trials, current version, EMA webpage.
2	*001-MCS-50-415_RD-01*: "TSAP annotations", current version; IDEA for CON.
3	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON.
4	*BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version; KMED.
5	*001-MCS-36-472: "*Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics*"*, current version; IDEA for CON.
6	*001-MCS-36-472_RD-01: "*Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies*"*, current version; IDEA for CON.
7	*001-MCS-50-415*: "Clinical Trial Data Analysis", current version; IDEA for CON.
8	*BI-KMED-BDS-HTG-410*: "Analysis and Presentation of Adverse Event Data from Clinical Trials ", KMED.
9	*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
Initial	**14-Jul-16**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct.
Final	**19-Nov-19**	[redacted]	None	This is the final TSAP.