Trial Statistical Analysis Plan

c01837068-03

BI Trial No.:	1315.1
Title:	A Phase I, open-label, cohort dose escalation trial with BI 836858 in patients with refractory or relapsed acute myeloid leukemia and patients with acute myeloid leukemia in complete remission with high risk to relapse Including: Protocol Amendment 1 [U11-3713-02] Protocol Amendment 2 [U11-3713-03] Protocol Amendment 3 [c02543230-04]
Investigational Product(s):	BI 836858
Responsible trial statistician(s):	 Telephone: Fax:
Date of statistical analysis plan:	09 APR 2018 REVISED
Version:	"Revised"

1 TABLE OF CONTENTS

LIST OF TABLES

2 LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
ATC classification	Anatomical, Therapeutic, Chemical classification
BI	Boehringer Ingelheim
BM	Bone marrow
BMI	Body Mass Index
BSA	Body Surface Area
BRPM	Blinded report planning meeting
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
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EoT	End-of-Text
ICH	International Conference on Harmonisation
iPV	Important protocol violation
IRR	Infusion related reaction
LLQ	Lower limit of quantification
LVSI	Laboratory values of special interest
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical and Quality Review Meeting

MTD	Maximum Tolerated Dose
NE	Not evaluable
PB	Peripheral blood
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
PKS	Pharmacokinetic set
PR	Partial remission
PT	Preferred term
PV	Protocol violation
REP	Residual effect period
RP2D	Recommended phase II dose
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listings
SOC	System organ class
SOP	Standard Operating Procedure
SS	Screened set
SSC	Special search category
TCM	Trial Clinical Monitor
TF	Treatment failure
TOC	Table of contents
TS	Treated set
TSAP	Trial statistical analysis plan
TTF	Time to treatment failure

3 INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This 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 (1).

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.

SAS Version 9.2 or later version will be used for all analyses.

Version 1 of this TSAP(c01837068-02) fully specified the planned analyses for the population of patients with refractory or relapsed AML. Further enrolment of this population was stopped as of 10-JUN-2016 (for more details refer to CTP amendment 3 and the authorisation letter to continue study cohort 3 in AML patients in complete remission with high risk to relapse). In January 2018, the trial was terminated because of low patient recruitment into the CR population. This version now includes the specifications as to how the data from the CR population will be summarized a final CTR that will includes the analyses for both populations.

4 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Clarification of Residual Effect Period (REP):

According to CTP section 6.2.5, for refractory or relapsed AML patients the reporting period for adverse events is defined until 6 weeks (42 days) after last administration of study drug.

However, the residual effect period (REP) for BI 836858 is defined as 30 days. Therefore, for all safety analyses defined in this TSAP, all events occurring between first drug administration until 30 days after last drug administration will be considered on treatment. A separate table or listing will be provided with adverse events outside the on-treatment period. See TSAP section 7.8 for details.

For AML patients in CR a REP of 30 days was defined in the CTP.

For the CR patients, an abbreviated set of tables and listings will be included consisting of:

- Patient disposition
- Patient demographics
- Baseline disease characteristics
- Exposure
- Medication compliance
- Summary table of Adverse Events
- Frequency table of adverse events by highest CTCAE grade
- Frequency table of user defined adverse events by highest CTCAE grade
- Overall summary of infusion related reactions
- Listing of patients with dose related toxicities
- A frequency table of AEs by treatment, system organ class, and preferred term
- Hepatic injury (DILI)
- Listing of hepatic enzymes and bilirubin
- Summary of haemalytic laboratory values

Listings of all clinical efficacy, safety, laboratory and biomarker data will be provided.

5 ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary endpoints are the maximum tolerated dose (MTD) and the number of patients with of dose limiting toxicity (DLT) during the MTD evaluation period.

Maximum tolerated dose (MTD):

MTD is defined as the highest dose studied for which the incidence of dose-limiting toxicity is no more than 17% (i.e., 1/6 patients) during the MTD evaluation period. The MTD will be defined on the basis of DLTs occurring during the MTD evaluation period of dose escalation cohorts. 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).

MTD evaluation period:

FOR PATIENTS WITH REFRACTORY OR RELAPSED AML,

the MTD evaluation period is defined as the time from the first administration of BI 836858 to start of the fifth administration, excluding the day of fifth administration. In case the fifth infusion will not be started, the evaluation period ends 30 days after the last administration.

FOR AML PATIENTS IN CR WITH HIGH RISK TO RELAPSE,

the MTD evaluation period is defined as the time from the first administration of BI 836858 to start of the third administration, excluding the day of third administration. In case the third infusion will not be started, the evaluation period ends 30 days after the last administration.

In case a patient 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, patients who have not completed the required number of administrations of BI 836858 for reasons other than BI 836858 related toxicity will be replaced.

That is, a patient will be considered evaluable for MTD assessment if he/she received at least 4 (refractory or relapsed patients) or 2 (patients in CR) administrations of BI 836858 or if he/she received less than 4 (refractory or relapsed patients) or 2 (patients in CR) administrations due to DLT.

The MTD estimate after the dose escalation part of the trial will be obtained on the basis of DLTs observed during the MTD evaluation period. However, for those patients who receive more than 4 (refractory or relapsed patients) or 2 (patients in CR) administrations of BI 836858, all AEs that constitute a DLT will be considered in the final determination of the dose recommended for Phase II.

The list of patients evaluable for MTD will be confirmed by the Trial Clinical Monitor (TCM) no later than at the last blinded report planning meeting (BRPM) before database lock (DBL) for the clinical trial report (CTR).

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoints

FOR PATIENTS WITH REFRACTORY OR RELAPSED AML:

Best overall response

The different categories possible for overall response (at a specific timepoint) are Complete remission (CR), Complete remission with incomplete blood count recovery (CRi), Partial remission (PR), Treatment failure (TF) (i.e. Resistant disease, Aplasia, Indeterminate cause, or morphologic relapse), Progressive disease (PD), and Not evaluable (NE).

Best overall response is defined as the best overall response (CR, CRi, PR, TF, PD or NE in this order) recorded since randomisation (first administration of trial medication in non-randomised trials) until the earliest of progressive disease (PD), death or last adequate disease assessment before new anti-cancer therapy.

In order to evaluate the best overall response, the investigator's assessment as given in the eCRF will be taken into account (no central review and no check versus bone marrow measurement is planned).

Progression free survival (PFS)

For patients with 'event' as outcome for PFS:

- PFS [days] = date of outcome - date of randomisation (date of first administration of trial medication in non-randomised trials) +1.

For patients with 'censoring' as outcome for PFS:

- PFS (censored) [days] = date of outcome - date of randomisation (date of first administration of trial medication in non-randomised trials) +1.

The censoring rules and dates of event or censoring for PFS under different scenarios are specified in Table 5.2.2:1.

Table 5.2.2: 1: Derivation rules for PFS

Situation	**Outcome (event or censored)**	**Date of outcome**
Progressed according to disease assessment	event	Date of disease assessment of progression
Death without progression	event	Date of death

Table 5.2.2: 1: Derivation rules for PFS (cont.)

Situation	**Outcome (event or censored)**	**Date of outcome**
Alive and not progressed	censored	Date of last disease assessment
No disease assessment performed post-baseline, vital status is unknown or patient is known to be alive	censored	Date of randomisation (or first treatment administration, in non-randomised trials)
Subsequent anti-cancer therapy before progression or death (check interval between start of new medication and earliest of subsequent PD or death)		
Interval <= 7 days	event	Earliest date of disease assessment of progression or death
Interval > 7 days	censored	Date of last disease assessment before initiation of subsequent anti-cancer therapy

Time to treatment failure (TTF)

As some patients will receive the next line of therapy, although no formal PD may be diagnosed at the time when the next treatment is indicated, the Time to treatment failure (TTF) will be derived similarly to PFS, but will consider PD, death or start of next anti-AML therapy as events.

For patients with 'event' as outcome for TTF:

- TTF [days] = date of outcome - date of randomisation (date of first administration of trial medication in non-randomised trials) +1.

For patients with 'censoring' as outcome for TTF:

- TTF (censored) [days] = date of outcome - date of randomisation (date of first administration of trial medication in non-randomised trials) +1.

The censoring rules and dates of event or censoring for TTF under different scenarios are specified in Table 5.2.2:2.

Table 5.2.2: 2: Derivation rules for TTF

Situation	**Outcome (event or censored)**	**Date of outcome**
Progressed according to disease assessment, no subsequent anti-cancer therapy	event	Date of disease assessment of progression
Death without progression, no subsequent anti-cancer therapy	event	Date of death
Subsequent anti-cancer therapy before progression or death	event	Date of first administration of subsequent anti-cancer therapy
Alive and not progressed, no subsequent anti-cancer therapy	censored	Date of last disease assessment
No disease assessment performed post-baseline, vital status is unknown or patient is known to be alive, no subsequent anti-cancer therapy	censored	Date of randomisation (or first treatment administration, in non-randomised trials)

FOR AML PATIENTS IN CR WITH HIGH RISK TO RELAPSE:

Progression free survival (PFS)

Defined as for refractory/relapsed AML patients, see above.

Time to treatment failure (TTF)

Defined as for refractory/relapsed AML patients, see above.

6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

In this Phase I trial, treatments are not randomised (open-label, dose escalation). Different dose levels of the investigational medicinal product can arise. The data will be presented for all dose cohorts separately, in particular patients will be analysed by the treatment group initially assigned in the first treatment course.

"Analysing treatment" will be used for reporting of treatment emergent adverse events (AE) and to differentiate between screening, on-treatment, post-treatment and post-study safety data. The inequalities start date ≤ onset date of AE < stop date will determine whether the AE will be assigned to the "analysing treatment" or not. Table 6.1: 1 defines the "analysing treatment period(s)" which will be used for reporting of treatment emergent AEs and safety laboratory parameters.

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
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 patient status obtained / last date patient known to be alive + 1 (if patient is lost to follow-up) / date of refusal + 1 day / the date patient died + 1	During the trial: open / empty; after database lock (DBL): DBL + 1 day
MTD evaluation period	Date of first administration of trial medication	For patients with refractory/relapsed AML: Date of fifth infusion or (if the fifth infusion was not administered) Date of last administration of trial medication + 30 days + 1 day For AML patients in CR: Date of third infusion or (if the third infusion was not administered) Date of last administration of trial medication + 30 days + 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.

In addition, to justify the MTD determination, AEs occurring during the MTD evaluation period will be presented separately from those occurring during the complete on-treatment period.

The actual treatment codes are defined in the document entitled "5-05-o-c-treatment-setup", which can be found in the trial's DMS Section 5 within BIRDS. Labels of each analysing treatment period and analysis numbers are provided in the TSAP technical documents "ADS Plan" and "Data guide".

6.2 IMPORTANT PROTOCOL VIOLATIONS

Even though no per protocol population is defined, patients with potentially important protocol violations (iPV) will be identified and documented.

Potentially important protocol violations are defined in Table 6.2:1. The final list of iPVs will be confirmed at the last blinded report planning meeting (BRPM) before the database lock at the time of the CTR.

Two separate iPV tables will be created for patients treated before and after the clinical hold and separately for patients with refractory/relapsed AML patients and AML patients in CR.

Table 6.2: 1 Important protocol violations

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	None
	A1.2	Patient has laboratory assessments that may cause additional risk.	EX 2, EX 8-11	None
	A1.3	Patient is unable to comply with the protocol	EX 14, EX 21	None
	A1.4	Patient has condition that may interfere with evaluation of safety (and/or efficacy)	EX 3-4, EX 6, EX 12, EX 13, EX15, EX 19, 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 1-3, EX 1, EX 5	None
B		**Legal criteria**		

Table 6.2: 1 Important protocol violations (cont.)

Category/ Code		Description	Comment/Example	Excluded from
	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 18	None
	B5	Patient's age < 18	IN 4	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
	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), see CTP section 4.1.4	None
	C3	Unjustified intra-patient dose-escalation	Create listing, decision at MQRM / RPM, see CTP section 4.1.4	None
	C4	Withdrawal of patient not performed according to CTP	Create listing, decision at MQRM / RPM, see CTP section 3.3.4	None
	C5	Discontinuation of trial drug not performed according to CTP	Create listing, decision at MQRM / RPM, see CTP section 3.3.4	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 (section 4.2.2.1 and exclusion criteria #3, #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 PATIENT SETS ANALYSED

- Screened set (SS): This patient set includes all patients who have signed the informed consent. The SS will be used for patient disposition tables.
- Treated set (TS): This patient set includes all patients who were documented to have received at least one dose of trial medication. The TS will be used for all efficacy and safety analyses.

- MTD evaluable set: The MTD set consists of all patients who were entered, treated and considered evaluable for MTD determination.

The above patient sets will be defined separately for refractory/relapsed AML patients and AML patients in CR. However, due to the early enrolment stop of the refractory/relapsed AML patients, the MTD (RP2D) set is not applicable for this patient population. No combined safety analysis of both patient populations is foreseen on trial level. If deemed necessary, this will be performed on project level.

No per protocol population will be used for analyses.

6.5 POOLING OF CENTERS

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

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 (2).

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 ANALYSES

The labelling and display format of statistical parameters will follow the guideline "Reporting of Clinical Trials and Project Summaries" (3).

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, and percentiles will be presented to one more decimal place than the raw data and SDs will be presented to two more decimal places. Minima and maxima will be presented to the same number of decimal places as the raw data.

For time-to-event analysis tables, the set of statistics is: Number of patients [N(%)], Number of patients with event [N(%)], Number of patients censored [N(%)], <Time to event> [<unit>] followed by P25 (25th percentile), median + CI, P75 (75th percentile). If not specified otherwise, the duration as well as the time to event will be displayed in months and a final decision will be made at the last RPM.

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 patients in 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.

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.

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 MedDRA version. Concomitant therapies will be coded according to WHO DD. Concomitant therapies (CT) 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 indication, there are often several classification alternatives. As appropriate, patients 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 ENDPOINTS

The primary endpoints are the MTD and the occurrence of DLT. The MTD is determined from the number of non-replaced patients with DLT during the MTD evaluation period (for the definition of MTD evaluation period refer to section 5.1).

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

Patients 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 patients will be provided. This will include the initial dose of the investigational medicinal product, patient 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 ENDPOINTS

7.5.1 Key secondary endpoint(s)

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

7.5.2 Other secondary endpoint(s)

Best overall response:

Best overall response will be analysed descriptively. The number of treated patients and the frequency of patients by best overall response category including the corresponding percentages will be presented.

Progression-free survival (PFS) and Time to treatment failure (TTF):

PFS and TTF will be assessed based on the Kaplan-Meier method. Point estimates together with confidence intervals (based on Greenwood's method) will be provided for median PFS (if applicable). The Breslow method for handling ties will be used. The censoring rules for PFS are as stated in Section 5.2.2.

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.

7.8 SAFETY ANALYSIS

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 patients 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 5 of the AE guideline (6).

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 patient, all episodes with the same preferred term (PT) (system organ class, SOC) will be condensed to one AE record 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 analyzing 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 'follow-up" (in randomised 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 5.2.2.1 as infusion related rections (IRRs) of CTCAE grade >= 3, DLTs (occurring during the MTD evaluation period or repeated treatment courses) and hepatic 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 patients with AEs by worst CTCAE grade.

The frequency of patients with adverse events will be summarised 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.

Patients 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 symtoms 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.

Fatal AEs:

AEs leading to death during the on-treatment period will be tabulated. Reported fatal AEs that occurred in the post-treatment phase will be listed.

Additionally, a table summarizing the information on deaths collected on the AE eCRF and the Patient Status eCRF will be provided.

User defined AE categories (UDAEC):

User defined AE categories (UDAEC) for adverse events are defined in in Table 7.8.1:1. For user defined AE categories which contain sub-searches and/or two sensitivity levels (broad and narrow) all possibilities will be displayed on the UDAEC level in tables, e.g. for infusion related reactions, tables will include the UDAECs “Infusion related reactions broad” and “Infusion related reactions narrow”, similarly for Bleeding: “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 (UDAEC) for Adverse Events

Topic	**UDAEC**	**MedDRA code**	**(Sub-)searches**	**Sensitivity**
Infusion related reactions	Infusion related reactions	20000021	SMQ Anaphylactic reaction + PT Infusion related reaction[1]	Narrow & broad (Algorithm)
Bleeding	Bleeding - SMQ Haemorrhage laboratory terms	20000040	SMQ Haemorrhage laboratory terms	Narrow & broad
	Bleeding - SMQ Haemorrhage terms (excl. laboratory terms)	20000039	SMQ Haemorrhage terms (excl. laboratory terms)	Narrow
Tumor lysis syndrome	Tumor lysis syndrome	20000219	SMQ Tumor lysis syndrome	Narrow & broad (Algorithm)

Table 7.8.1: 1: Definition of user defined AE categories (UDAEC) for Adverse Events (cont.)

Nausea	Nausea		BIcMQ	Narrow & broad
Vomiting	Vomiting		BIcMQ	Narrow & broad
Drug related hepatic disorders	Drug related hepatic disorders	20000006	SMQ Drug related hepatic disorders plus the following sub-searches:	Narrow & broad
	Drug related hepatic disorders - SMQ Cholestasis and jaundice of hepatic origin	20000009	Cholestasis and jaundice of hepatic origin (SMQ)	Narrow & broad
	Drug related hepatic disorders -SMQ Drug related hepatic disorders - severe events only	20000007	Drug related hepatic disorders - severe events only (SMQ)	Narrow & broad
	Drug related hepatic disorders - SMQ Liver related investigations, signs and symptoms	20000008	Liver related investigations, signs and symptoms (SMQ)	Narrow & broad
	Drug related hepatic disorders - SMQ Liver-related coagulation and bleeding disturbances	20000015	Liver-related coagulation and bleeding disturbances (SMQ)	Narrow & broad

Table 7.8.1: 1: Definition of user defined AE categories (UDAEC) for Adverse Events (cont.)

Cardiac safety	Cardiac safety - Cardiac failure (tailored SMQ)[2]	20000004	Cardiac failure (tailored SMQ)[2]	
	Cardiac safety - SMQ Cardiac arrhythmia	20000049	SMQ Cardiac arrhythmia	Broad
	Cardiac safety - SMQ Ischemia heart disease	20000043	SMQ Ischemia heart disease	Broad
ALT	ALT		BIcMQ Elevated Specific Liver Function Parameters sub-search1	Narrow & broad
AST	AST		BIcMQ Elevated Specific Liver Function Parameters sub-search2	Narrow & broad
ALKP	ALKP		BIcMQ Elevated Specific Liver Function Parameters sub-search3	Narrow & broad
Bilirubin	Bilirubin		BIcMQ Elevated Specific Liver Function Parameters sub-search5	Narrow & broad
Neutropenia[3]	Neutropenia		BIcMQ[3]	Broad

[1] The PT Infusion related reaction as collected in the eCRF will be included on both sensitivity levels (broad and narrow).

[2] 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.

[3] Neutropenia as defined by the BIcMQ “Haematopoietic Cytopenias”, Subsearch1.1.

Table 7.8.1: 2: User defined AE category (UDAEC) Cardiac Failure

Selected PTs for Cardiac Failure
Cardiac asthma
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

7.8.2 Laboratory data

The analyses 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 AEs will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses.

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 version 4.03. 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 during the on-treatment phase, and from baseline to last laboratory value.

Patients with missing CTCAE grade at baseline or no baseline value but post baseline values will be displayed in the category "Missing CTCAE grade at baseline".

Possible clinically significant abnormal laboratory values:

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. For those parameters for which no CTCAE has been defined, BI standard definition will be used to determine possible clinical significance. Frequency of patients with possible clinically significant abnormal laboratory values will be provided whenever applicable. If no baseline value is available but the patient 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

In addition, the following definition of potential Hy's law cases was discussed with the FDA at the Pre-NDA meeting of the NSCLC submissions of the nintedanib trials 1199.13 and 1199.14 and was agreed by the authorities. Please also refer to the FDA guideline Guidance for Industry Drug- Induced Liver Injury: Premarketing Clinical Evaluation, version of July 2009.

These are defined as those cases where a combination of all of the following events occurred: any on-treatment value of ALT or AST (or both) > 3 times upper limit of normal (3 x ULN) with total bilirubin ≥ 2 x ULN and ALKP < 2 x ULN. 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.

All of the above combinations of elevated liver enzymes will be analysed, i.e. DILI cases as defined in the CTP and additionally the definition of potential Hy's law cases which was discussed with the FDA by the nintedanib project.

Handling of laboratory parameters with CTCAE grade -1:

For Uric Acid, Glomerular filtration rate (GFR) and Hypokalemia, the CTCAE grade cannot always be assigned by the laboratory parameter itself as two different CTCAE grades have the same laboratory constellation, but are distinguished by additional clinical parameter. In this case a CTCAE grade of "-1" will be assigned initially. For all analyses patients with a CTCAE grade of "-1" will be treated as

- Grade 1 for Uric Acid
- Grade 3 for GFR
- Grade 1 for Hypokalemia (Only when CTCAE version 4.03 is used)

Handling of Urine protein (UPROZ)

With CTCAE version 4, the CTCAE grade 3 for proteinuria is defined based on 24 hrs values [g/24 hrs] only; no dipstick definition is available based on quantitative results.

High values of UPROZ (+++, ++++; labstd = 3, 4) would therefore be assigned to CTCAE grade -9, which by default is equivalent to CTCAE grade 0. To circumvent this, high values of UPROZ (+++, ++++; labstd = 3, 4) will be assigned to CTCAE grade 2.

7.8.3 Vital signs

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

7.8.4 ECG

12-lead resting ECGs are done throughout the trial and are assessed for clinically relevant results which are to be recorded as either concomitant disease or AE by the Investigator. No further ECG analysis is planned.

8 REFERENCES

1 *001-MCG-160_RD-01*: "TSAP annotations", current version; IDEA for CON.

2 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

3 *001-MCG-159*: “Reporting of Clinical Trials and Project Summaries”, current version; IDEA for CON.

4 *001-MCS-36-472: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics"*, current version; IDEA for CON.

5 *001-MCS-36-472_RD-01: “*Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies*”*, 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.

10 HISTORY TABLE

Table 10: 1 History table

Version	**Date (DD-Mmm-YY)**	**Author**	**Sections changed**	**Brief description of change**
Final	**14-July-16**		None	This is the final TSAP without any modification
Revision	**09-Apr-18**		4	Added specifications for final report to include CR patients