Trial Statistical Analysis Plan

c20741038-03

BI Trial No.:	1200.120
Title:	Phase I/II open label, dose escalation trial to determine the MTD, safety, PK and efficacy of afatinib monotherapy in children aged ≥1 year to <18 years with recurrent/refractory neuroectodermal tumours, rhabdomyosarcoma and/or other solid tumours with known ErbB pathway deregulation regardless of tumour histology Including Protocol Amendment 1 (c02332639-03), 2 (c02332639-04) and 3 (c02332639-05)
Investigational Product(s):	Giotrif®, Gilotrif®, Afatinib Capsules and Solvent for Oral Solution
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	31 JUL 2020 REVISED
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AUC	Area Under Curve
BMI	Body mass index
BRPM	Blinded report planning meeting
BSA	Body surface area
BUN	Blood urea nitrogen
C_{max}	Maximum Concentration
CR	Complete Response
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DLT	Dose Limiting Toxicity
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DoR	Duration of objective response
DRA	Drug Regulatory Affairs
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
INRC	International Criteria for Neuroblastoma Response Criteria
IPD	Important protocol deviation
LVEF	Left ventricular ejection function
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MTD	Maximum Tolerated Dose
MxR	Mixed response
NOR	Not-valid results
NOS	No sample available
NR	No response
O*C	Oracle Clinical
OR	Objective Response

Term	Definition / description
PD	Progressive Disease
PFS	Progression free survival
PK	Pharmacokinetics
PopPK	Population Pharmacokinetic(s)
PPS	Per protocol set
PPSR	Proposed pediatric study request
PR	Partial Response
PSTAT	Project Statistician
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
SAS	Statistical Analysis System
s.d.	Standard deviation
SD	Stable Disease
SMQ	Standardised MedDRA query
SOC	System Organ Class
t_{max}	Time to reach maximum concentration
TCM	Trial Clinical Monitor
TMW	Trial Medical Writer
TOC	Table of contents
TSAP	Trial Statistical Analysis Plan
TSTAT	Trial Statistician
VGPR	Very good partial response

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 its amendments, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The clinical trial protocol (CTP) v3 was amended based on the feedback received from the FDA during a PPSR request. The MTD expansion cohorts will now recruit up to 38 patients evaluable for OR based on biomarker selection criteria as well as specific tumour indications.

The definition of duration of objective response was misspecified in the CTP as the interval between the date of randomization and the earliest date of disease progression. The correct definition is clarified in Section 5.2.2 of this TSAP as the time from first documented response of CR, VGPR, PR, or MxR until the earliest of disease progression or death among patients with objective response.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

Dose finding part:

- The primary endpoint is the **dose limiting toxicity** (DLT) measured during the first course of treatment. DLTs are defined in Table 4.1.4.1.2 of the CTP.
- **Pharmacokinetics** ($AUC_{\tau,ss}$, $C_{max,ss}$)

The primary objective of the dose finding part is to determine the maximum tolerated dose (MTD) of the study drug as defined by patients with DLT in a paediatric population. The MTD will be determined as the highest dose at which no more than 1/6 patients experienced DLT. The MTD evaluation period is defined as the initial 28 days of study treatment. Patients who developed DLT at any time during the initial 28 treatment days and patients who have completed the MTD evaluation period without missing more than 25% of the afatinib doses regardless of the reason will be referred to as patients evaluable for DLT.

MTD expansion cohort part:

- **Objective response** (OR) by investigator assessment according to the institutional response evaluation criteria for the given tumour type, assessed every 8 weeks until progression of disease.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

There were no key secondary endpoints for this study.

5.2.2 Secondary endpoint(s)

Dose finding part:

- **Objective response** (OR) assessed by investigator according to the institutional response evaluation criteria for the given tumour type, assessed every 8 weeks until progression of disease
- **Pharmacokinetics** (AUC_{0-24}, C_{max}, $t_{max(,ss)}$ and accumulation (or effective) half-life)

MTD expansion cohort part:

- **Progression free survival** (PFS) is defined as the duration of time from the date of first drug administration to the date of the first documented disease progression evaluated according to institutional response criteria or to the date of death from any cause, whichever occurs first. Censoring rules and dates of outcome for PFS under difference scenarios are specified in Table 5.2.2: 1.
- **Duration of objective response** (DoR) is defined as the time from first documented response of CR, VGPR, PR, or MxR until the earliest of disease progression or death among patients with objective response. Censoring rules and dates of outcomes follow the same specifications as for PFS in Table 5.2.2: 1 for applicable scenarios.
- **Pharmacokinetics** ($AUC_{\tau(,ss)}$, $C_{max(,ss)}$, $t_{max(,ss)}$ and accumulation (or effective) half-life)

Table 5.2.2: 1 Censoring rules and determination of date of event or censoring for PFS

Situation	**Outcome (event or censored)**	**Date of outcome**
No baseline radiological assessment (no death before second scheduled radiological assessment)	censored	Date of first treatment administration
Death without progression. At most one missed radiological assessments, i.e. at most 112 days between death and last assessment (or treatment start date if no post-baseline assessments).	event	Date of death
Death without progression. Two or more missed radiological assessments, i.e. longer than 112 days between death and last assessment (or treatment start date if no post-baseline assessments).	censored	Date of last radiological assessment / Date of first treatment administration if no post-baseline assessments
No radiological assessment performed post-baseline, vital status is unknown or patient is known to be alive	censored	Date of first treatment administration
Progressed according to radiological assessment. At most one missed radiological assessments, i.e. at most 112 days between progression and last assessment before progression.	event	Date of radiological assessment of progression
Progressed according to radiological assessment, i.e. longer than 112 days between progression and last assessment before progression.	censored	Date of last radiological assessment before progression
Alive and not progressed (irrespective of missed radiological assessments)	censored	Date of last radiological assessment
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent anti-cancer therapy started prior to a death	censored	Date of first treatment administration

For further details on endpoints, please see CTP Section 5.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Daily single oral doses of afatinib will be investigated in this study for paediatric patients. Dose escalation starts at 80% of the adult MTD by m^2 BSA and allometric scaling (Level 0) and can be escalated to 100% (level 1), 125% (level 2) and 150% (level 3) of the adult dose if required. In case level 0 exceeds the MTD, a dose level -1 will allow de-escalation to 50% of the adult MTD dose by m^2 BSA and allometric scaling. Oral solution is available for younger children and patients who cannot swallow afatinib film coated tablets.

Analysing treatment periods are defined in Table 6.1: 1 for reporting of treatment emergent AEs and safety laboratory data. An adverse event will be assigned to the analysing period where start date ≤ onset date of AE < stop date.

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 intake of study drug
Course 1	Date of first intake of study drug	Start date of Course 2, or date of first intake of study drug + 28 days if the patient did not start Course 2
On-treatment	Date of first intake of study drug	Date of last intake of study drug + 29 days
Residual effect period (REP)	Date of last intake of study drug + 1 day	Date of last intake of study drug + 29 day
Off-treatment	Date of last intake of study drug + 29 day	Date of last follow up visit + 1 day or date of death + 1 day whichever occurred first

The residual effect period (REP) for afatinib is 28 days after last intake of afatinib. Data recorded between the first study drug intake until up to 28 days after the last study drug intake will be considered as on-treatment.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation is important if it affects the rights or safety of the study patients, or if it can potentially influence the primary outcome measurements in a non-negligible way. Patients with important protocol deviations (IPDs) that could potentially impact the evaluation of the primary endpoint(s) will be excluded.

The different categories of IPDs are defined in Table 6.2: 1. IPDs will be reviewed at Medical Quality Review Meetings (MQRMs) conducted periodically during the trial. A list of protocol deviations will be discussed at the report planning meetings (RPMs). If the data show other IPDs, this table will be supplemented accordingly at MQRMs or RPMs or through team review of the protocol deviation log. The decision whether a patient will be excluded from the analysis will be made at the final RPM prior to DBL.

Table 6.2: 1 Important protocol deviations

Category/ Code		Description	Comment/Example	Excluded from	Manual/ Automatic
A		**Inclusion/Exclusion Criteria**			
	A1				
	A1.1	Laboratories measurements	Exclusion criteria13,14,15	None	Automatic
	A1.2	Forbidden concomitant diagnoses	Exclusion criteria 4,5,7,9,10,11,12	None	Automatic
	A1.3	Female patients who are pregnant or doing breast feeding at baseline	Exclusion criteria 6	None	Automatic
	A1.4	Prohibited concomitant medications, radiotherapy and surgery	Exclusion criteria 1,2,3, 8	None	Automatic
	A2				Automatic
	A2.1	Patient does not have trial diagnosis	Inclusion criteria 1	None	Automatic
	A2.2	Patient did not recover (to CTCAE grade 1 or baseline) from any acute toxicity resulting from prior anti-cancer treatment (except alopecia)	Inclusion criteria 4	None	Automatic
	A2.3	Patient did not have Lansky/Karnofsky (depending on age) scores >=50% assessed within 2 weeks prior to enrolment.	Inclusion criteria 8	None	Automatic
	A2.4	Patient has LVEF <50%	Inclusion criteria 12	None	Automatic
	A2.5	Required ErbB pathway deregulation absent	MTD Expansion Cohort: Inclusion criteria 1or 13	None	Automatic
	A2.6	Patient age at study start not between >=2 to <18 years Patient age at study start not between >=1 to <18 years	Dose finding cohort: Inclusion criteria 3 MTD expansion cohort: Inclusion criteria 3	None	Automatic
	A2. 7	No tumour tissue available (exception of DIPG)	MTD Expansion Cohort: Inclusion criteria 7	None	Automatic
	A2.8	Patient do not have at least one measurable lesion according to the institutional response criteria for the given tumour type.	Inclusion criteria 14	None	Automatic

Table 6.2: 1 Important protocol deviations (cont.)

Category/ Code		Description	Comment/Example	Excluded from	Manual/ Automatic
B		**Informed Consent**			Automatic
	B1	Informed consent not given	Inclusion criterion 6	All	Automatic
	B2	Informed consent after administration of trial medication	Inclusion criterion 6	None	Automatic
	B3	Informed consent not in accordance with regulations		None	Manual
C		**Trial Medication**			
	C1	Dose change of afatinib not according to protocol		None	Manual
	C2	Non-compliance	Afatinib not taken according to protocol	None	Manual
	C3	Dose reduction/paused/discontinuation not according to protocol following an AE/DLT	Refer to Table 4.1.2.3:1 and Table 4.2.2.1:1 in the CTP	None	Manual
D		**Concomitant Treatment**			
	D1	Any other chemotherapy, immunotherapy or radiotherapy during the trial except for palliative radiation	Refer to Section 4.2 of the CTP	None	Manual
	D2	During palliative radiation, treatment was not paused until the patient recovered from any radiation associated toxicity	Refer to Section 4.2 of the CTP	None	Manual
	D3	Continuous interruption of >28 days due to palliative radiotherapy	Refer to Section 4.2 of the CTP	None	Manual
E		Critical study procedure			
	E1	Critical study procedure not followed		None	Manual
F		Privacy / data protection			
	F1	Privacy and/or data protection violated		None	Manual

6.3 PATIENT SETS ANALYSED

Treated set (TS):

This patient set includes all patients enrolled in the trial who were documented to have taken at least one dose of study medication.

Dose finding cohort treated set:

This patient set includes all patients enrolled in dose finding cohort of the trial who were documented to have taken at least one dose of study medication.

MTD Expansion cohort treated set:

This patient set includes all patients enrolled in expansion cohort who must satisfy the following criterion:

- Patients' tumour must be tested for positivity on 2 of the following tests: EGFR IHC>150 and/or HER2 IHC>0 and/or EGFR FISH positive and/or HER2 DDISH positive.

or

- Patient will have proven genomic, transcriptomic or proteomic alterations which are not defined above.

and

- Patients who were documented to have taken at least one dose of study medication.

PK analysis set (PKS):

This set includes all patients in the treated set (TS) who provided 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. Thus, a patient will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

6.5 POOLING OF CENTRES

This section is not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards (3). Missing efficacy data, including vital status, tumour imaging data, will not be imputed in general. All reasonable efforts have been undertaken during the study to obtain such data.

Missing or incomplete drug stop dates are imputed as follows:

- If month and year known for drug stop date but day missing, then use date of death if within the month; otherwise use last day of month.
- If both month and day unknown, then use the first available date in this order: date of death, date of last contact, last day of the month of last visit.

Missing data and outliers of PK data are handled according to (2). Samples marked as no sample available (NOS) or non-valid result (NOR) will not be included in the analysis. Please refer to Sections 7.3.5 and 7.4 of the CTP for more details.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Study days and visits will be labelled according to the flow chart of the CTP.
Unless otherwise specified, baseline is defined as the latest time point before the very first administration of any study medication. If this criterion is not fulfilled, then no baseline will be derived. Note that for some trial procedures (for example performance score, body weight, vital signs, laboratory tests) this may be the value measured on the same day when trial medication was started. In these cases it will be assumed that the measurements were taken prior to the intake of any study medication. For laboratory values 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 study 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 study drug administration. If any of these times are missing and the date of laboratory value is equal to the date of first study drug administration, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

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.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT(S)

7.4.1 Dose Finding Part:

One of the primary objectives is to assess the MTD based on the number of patients presenting DLTs during the MTD evaluation period. Therefore, an overall summary of DLTs (see CTP Section 4, Table 4.1.4.1.2 for the definition of DLTs) which occurred during the MTD evaluation period will be provided for each dose cohort from the dose finding cohort treated set. Patients who were replaced within the MTD evaluation period will be excluded from the determination of the MTD but will be considered for all other safety evaluations.

A summary of the number of patients with DLTs overall in any course will be also given by initial treatment and displayed in a similar format to the summary of DLTs occurring in the MTD evaluation period.

The determination of the MTD is based on a Rolling 6 design as illustrated in Section 4, Table 4.1.4.1:1 of the CTP. The MTD is defined as the highest dose at which no more than 1/6 patients experienced DLT considered related to afatinib during the MTD evaluation period. Refer to CTP 7.3.1 for further details on MTD evaluation.

Analysis of the standard PK endpoints is performed according to (2) and (8) as outlined in Section 7.3.5 of the CTP.

7.4.2 MTD expansion cohort part:

Objective response (OR) is defined as a best overall response of complete response (CR) or partial response (PR) based on investigator's assessment according to the institutional

response evaluation criteria for the given tumour type. If the International Criteria for Neuroblastoma Response Criteria (INRC) is used, OR is defined as complete response (CR), very good partial response (VGPR), partial response (PR) and mixed response (MxR). For further details on OR, please refer to CTP Section 7.3.1. The objective response rate will be calculated and reported as proportion of responders with 95% Clopper-Pearson CIs based on all treated patients. Objective response will be summarized regardless of confirmation.

Additional summary or listing may be provided for confirmed response. If only few patients (fewer than 5) achieved objective response, a detailed listing will be reported.

For objective responses, evaluated by institutional response evaluation criteria other than INRC, below confirmation rule for best overall response will be considered.

- If CR or PR: look at all subsequent visits, if there is another CR or PR >=28 days then the patient has a confirmed response. If there is not another CR or PR >=28 days then the patient can be SD. Please note that once patient achieve CR any response other than CR will be considered as PD.

Detailed specifications are listed in Table 7.4.2: 1.

Table 7.4.2: 1 Confirmation rule for best overall response

Overall response (time point 1)	Overall response (subsequent time point)	Unconfirmed best overall response	Confirmed best overall response
CR	CR (>=28 days from 1)	CR	CR
CR	CR (< 28 days from 1)	CR	SD
CR	PR[1]	CR	SD
CR	SD	CR	SD
CR	PD	CR	SD
CR	NE/Missing	CR	SD
PR	CR (>=28 days from 1)	CR	PR
PR	CR (< 28 days from 1)	CR	SD
PR	PR (>=28 days from 1)	PR	PR
PR	PR (< 28 days from 1)	PR	SD
PR	SD	PR	SD
PR	PD	PR	SD
PR	NE/Missing	PR	SD

1= If truly a CR at first response, any subsequent disease (even a PR relative to baseline) makes the disease PD. Could only be a PR if initial CR is changed to PR (i.e. not a true CR).

For INRC, a similar derivation of confirmed response will apply. That is, a subsequent assessment with the same or a better overall response on or after 28 days is required for the confirmation of an objective response, in the order from best to worst of CR > VGPR > PR > MxR. Otherwise, a SD will be considered as the confirmed best overall response.

7.5 SECONDARY ENDPOINT(S)

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)

For progression free survival (PFS), objective response (OR) and duration of objective response (DoR), a descriptive and graphical summary of the endpoint will be provided. The Kaplan-Meier estimates of PFS and DoR (if applicable) and 95% confidence intervals will be calculated at the time of each planned assessment. For the dose finding part, the number of patients with OR will be summarized by dose level. If fewer than 5 patients achieved OR, then DoR will only be listed; Kaplan-Meier estimates will not be calculated and no summary table or graph will be provided.

To evaluate the potential influence of age on pharmacokinetic parameters like C_{max} and AUC, an exploratory subgroup analysis will be performed for different age groups. For this, binning of age into groups will be performed to ensure that groups have reasonable patient numbers. If feasible, a correlation of age and PK parameters may be performed.

7.7 EXTENT OF EXPOSURE

Treatment exposure will be primarily summarized by the total on-treatment time and has been defined in Section 5.4 of this TSAP.

Treatment interruptions before permanent discontinuation will not be excluded. Summary statistics for treatment time by each dose level of afatinib over time will also be provided.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

The analyses of adverse events (AE) will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. For analysis of duration, severity etc. of multiple AE occurrences, data on the case report form (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 two 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 onsets of the occurrences, but no deterioration was observed for the later occurrence.

For further details on summarization of AE data, please refer to the BI guideline (4).

The analyses of adverse events will be based on the concept of treatment-emergent adverse events. That means that all adverse events occurring between first drug intake and 28 days after last drug intake or death, whichever occurs first, will be assigned to the on-treatment period. All adverse events occurring before any study drug intake will be assigned to 'screening' and all adverse events occurring after last study drug intake + 28 days will be assigned to 'Off-treatment' (for listings only). For details on the treatment definition, see Section 6.1.

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarised by highest CTC grade (grades 1, 2, 3, 4, 5 and all grades), treatment, primary system organ class and preferred term for each of the following AE tables as well as relatedness of AEs to treatment and seriousness:

- DLTs (1st course and all courses)
- All AEs
- Drug-related AEs
- AEs leading to dose reduction
- AEs leading to treatment discontinuation
- Drug-related AEs leading to dose reduction
- Drug-related AEs leading to treatment discontinuation
- AEs leading to death
- Serious AEs
- Drug related serious AEs
- Other significant AEs, defined as AEs leading to dose reduction or permanent discontinuation of study medication
- Non-serious AEs with higher than 5% occurrence rate for disclosure on ClinicalTrials.gov

Please refer to CTP Section 5.2.2.1 for definitions of the adverse events. All tables will be sorted by system organ classes (SOC) according to the standard sort order specified by the European Medicines Agency (EMA). Preferred terms (PTs) will be sorted by frequency (within SOC).

The table for all AEs will be repeated with the project defined grouping of AE terms (acute renal failure associated with severe diarrhoea, acne, rash, stomatitis, conjunctivitis, paronychia, severe cutaneous adverse reactions, interstitial lung disease, keratitis, hepatic impairment, pancreatitis, heart failure, gastrointestinal perforation, hypersensitivity reactions, nail disorders and fatigue). Details of the project defined groupings will be defined in the technical TSAP. In these tables the grouped AEs will replace the original PTs for all AEs that are included within the grouped term. The grouped AE categories will then be tabulated along with all remaining MedDRA PTs, sorted by descending frequency.

A reference table presenting the entire project defined groupings and MedDRA PTs within each grouping will also be produced.

Additional AE tables will be produced for AEs of special interest (hepatic injury as defined in CTP Section 5.2.2.1 and dose limiting toxicities as defined by CTP Section 4, table 4.1.4.2). Listings providing further details on highest CTC grade, action taken with study drug and time to first onset of AE will be produced.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5). The same on-treatment period as considered for the analysis of AEs will be applied for laboratory values. CTC grade for applicable lab parameters will be calculated according to CTCAE v3.0 (7).

For a list of laboratory parameters considered for this trial, please refer to CTP Section 5.2.3, Table 5.2.3:1. Descriptive statistics of all normalized laboratory values by visit will be provided including changes from baseline. Transition tables of CTCAE grade from baseline to worst value and last value on treatment, and frequency tables of possible clinically significant abnormalities will be produced. For those parameters that have CTC grading possible clinically significant abnormalities are defined as those laboratory values with a CTC grade ≥ 2 that have had an increase of ≥ 1 grade from baseline. For those parameters for which no CTC grade has been defined standard BI project definitions will be used to decide on clinical significance. See Tables 7.8.2: 1 and 7.8.2: 2 for the potential clinical significance rules.

Analyses of descriptive statistics will use normalized lab values (variables ULN, LABN). Analyses of frequencies of patients with potential clinical significance, analyses of shift, and liver function categories tables will use converted values (ULC, LABSTD).

Summaries will be produced of laboratory data recorded on-treatment. Listings will be provided for data recorded prior to treatment, on-treatment and post-treatment. For details on the treatment definition, see Section 6.1.

For the primary laboratory parameters listed in Table 7.8.2: 1, full analysis of descriptive statistics, transition tables and possible clinical significant abnormalities will be conducted.

Analysis of secondary laboratory parameters listed in Table 7.8.2: 2 will be limited to frequency tables of possible clinically significant abnormalities. Listings of converted and normalized values for all laboratory parameters considered for this trial will be provided in Appendix 16.2 of the CTR.

Table 7.8.2: 1 Primary laboratory parameters

Label	Lab test name	Direction of interest	Potential clinical significance rule
ALKP	Alkaline phosphatase	High	A[1]
APTT	APTT (Activated partial thrombopl. time)	High	A[1]
CRE	Creatinine	High	A[1]
CRECL	GFR/Creatinine clearance	Low	A[1, 2]
HGB	Haemoglobin	Low	A[1]
INR	PT-INR	High	A[1]
K	Potassium	Low	A[1]
LYMPH	Lymphocytes	Low	A[1]
NA	Sodium	Low	A[1]
NEUT	Neutrophils	Low	A[1]
SGOT	AST/GOT, SGOT	High	A[1]
SGPT	ALT/GPT, SGPT	High	A[1]
TBILI	Bilirubin, total	High	A[1]
WBC	White blood cell ct.	Low	A[1]

[1]A = CTCAE grade 2 or greater with an increase of at least one CTCAE grade from baseline.
[2]Values less than 0.25xLLN will be assigned CTCAE grade 3.

Table 7.8.2: 2 Secondary laboratory parameters

Label	Lab test name	Direction of interest	Potential clinical significance rule
BUN	Blood urea nitrogen	High	> 10
CA	Calcium	Low & High	A[1]
CK	Creatine kinase	High	A[1]
GLUB	Glucose	Low & High	A[1]
LDH	LDH	High	≥ 3xULN
TPRO	Protein, total	Low & High	< 45, > 100
UREA	Urea	High	> 1.5xULN
URIC	Uric acid	High	A[1, 3]

[1]A = CTCAE grade 2 or greater with an increase of at least one CTCAE grade from baseline.
[3]Values >ULN – 10 mg/dL or ≤0.59 mmol/L will be assigned CTCAE grade 1.

7.8.3 Vital signs

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

7.8.4 ECG

ECG data will be collected as described in CTP Section 5.2.4. Clinically significant findings in ECG data will be reported under "Adverse events" if applicable and will be analysed accordingly.

7.8.5 Others

Left ventricular ejection function:

Left ventricular ejection function (LVEF) will be assessed by echocardiography (ECHO) as specified in the CTP Section 5.2.5.2.

Attainment of steady-state:

Attainment of steady-state will be assessed graphically.

8. REFERENCES

1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED
3	*BI-KMED-BDS-HTG-0035:* "Handling of Missing and Incomplete AE Dates", current version; KMED
4	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED
5	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED
6	*BI-KMED-BDS-QRG-0011*: "BI Lab Standards", current version; KMED
7	Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, published: August 9, 2006; U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute.
8	*BI Position Paper 3.8*: Statistical Methods for PK, current version.

10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP.

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**17-JAN-18**		None	This is the final TSAP without any modification
Revised	**14-JUL-20**		All	dded disease control as additional secondary endpoint. Section 5: Aligned endpoint definitions with protocol. Added censoring rules for PFS. Section 6: Clarified definitions of analysis treatment periods. Updated definitions of important protocol deviation. Updated definition of PK analysis set. Section 7: Added confirmation rule for best overall response. Clarified analysis of DoR when number of patients with OR is low. Updated analysis plan for adverse events and safety laboratory data. Added attainment of steady state analysis. Section 8: Updated references to current company guidelines.
Revised	**31-JUL-20**		Sections 4 and 5.2.2	The definition of "Duration of objective response", a secondary endpoint, was incorrect in the CTP. A clarification is added in Section 4. The correct definition is provided in Section 5.2.2.