BAL101553

STATISTICAL ANALYSIS PLAN

CDI-CS-004

Phase I Study to Determine the Safety and Tolerability of the Oral Microtubule Destabilizer BAL101553 in Combination with Standard Radiation in Patients with *MGMT* Promoter Unmethylated Newly Diagnosed Glioblastoma

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DOCUMENT APPROVAL

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Study title:	Phase I Study to Determine the Safety and Tolerability of the Oral Microtubule Destabilizer BAL101553 in Combination with Standard Radiation in Patients with *MGMT* Promoter Unmethylated Newly Diagnosed Glioblastoma
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Sponsor:	Basilea Pharmaceutica International Ltd, Allschwil 487 Hegenheimermattweg 167b CH-4123 Allschwil/Switzerland Tel + 41 61 606 1111

Name/Title	Date	Signature
[redacted]		

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LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence interval
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
FAP	Full analysis population
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
OS	Overall Survival
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PT	Preferred Term
RT	Radiotherapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class

1 INTRODUCTION

This statistical analysis plan (SAP) specifies the detailed procedures for performing the statistical analyses and producing tables, listings, and figures in the study described in Basilea Pharmaceutica International Ltd. (Basilea) Protocol ABTC-1601. The version of the protocol at the time of preparation of this SAP is dated 14 January 2022.

At the time of writing this document, the study is ongoing.

2 STUDY OBJECTIVES, ENDPOINTS AND DESIGN

2.1 Study Objectives

2.1.1 Primary objective

The primary objectives of this study is to determine the maximum tolerated dose (MTD) of BAL101553 in combination with standard radiation in patients with newly diagnosed *MGMT* promoter unmethylated GBM.

2.1.2 Secondary objectives

The secondary objectives are:

- To estimate safety and tolerability of BAL101553 in combination with standard radiation in patients with newly diagnosed *MGMT* promoter unmethylated GBM.
- To determine overall and progression-free survival.
- To assess the pharmacokinetics (PK) of BAL101553 and BAL27862.
- To explore expression of tissue biomarkers, including BubR1, stathmin, and EB1 at baseline (exploratory biomarkers).

2.2 Study Endpoints

2.2.1 Primary endpoint

The primary study endpoint is the frequency and characteristics of dose-limiting toxicities (DLT), which are relevant for determination of the MTD of BAL101553.

2.2.2 Secondary endpoints

Secondary endpoints are:

- Safety/Toxicity:
  - Incidence, frequency, severity, type, and relationship of adverse events (AEs) and serious AEs (SAEs)
  - Changes in laboratory tests, vital signs, and electrocardiogram (ECG) data.

  NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 or 5.0 is used for scoring toxicity and adverse events.
- Efficacy endpoints:
  - Overall survival (OS).

  - Progression-free survival (PFS).
- PK variables calculated using noncompartmental analysis for BAL101553 (if applicable) and for BAL27862 will comprise: C_{max}, T_{max}, AUCs, and if possible t1/2, systemic clearance, and volume of distribution. The PK dose proportionality will also be assessed
- Expression of BubR1, stathmin, and EB1 at baseline (exploratory biomarker) will be addressed separately.

2.3 Study design

This is a phase 1, open-label, multicenter, dose-finding study of BAL101553 when given in combination with radiotherapy (RT) in patients with newly diagnosed *MGMT* promoter unmethylated GBM. All subjects must have had histological confirmation of GBM, either by biopsy or by resection.

Following tumor resection, patients will begin an assigned BAL101553 dose in combination with the standard 6 weeks of radiation.

Oral BAL101553 will be given once daily (7 days a week) for 6 weeks, concurrent with standard RT. This will be followed by a 4-week no-treatment period. The duration of study treatment will be defined as these 6 weeks of treatment plus 4 weeks of rest. The safety data will be collected during this entire period.

After the 4-week rest period following the 6 weeks of treatment, patients will be off study treatment and should continue standard-of-care treatment with adjuvant temozolomide and appropriate follow-up.

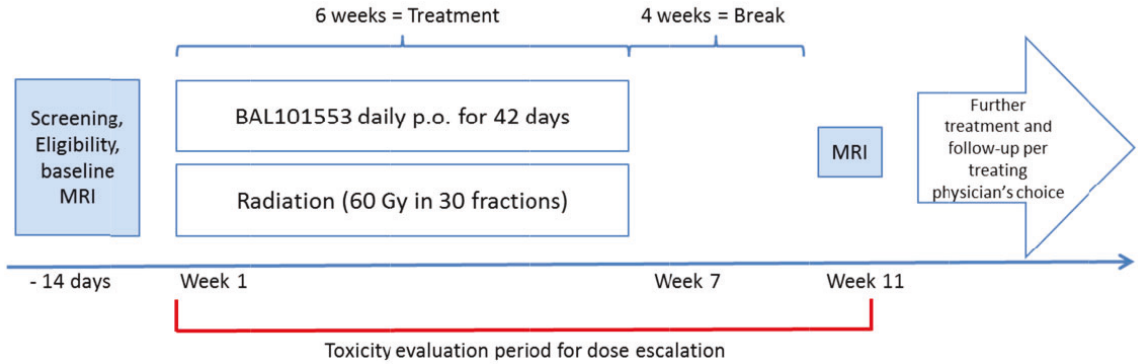

Figure 1: Study design schema

A modified 3+3 design will be used for dose-finding (see protocol for details). To prevent unreasonable delay in completing each cohort, 5 patients will be enrolled onto a dose cohort to ensure 3 evaluable patients at the end of the 10-week treatment period. It is planned to test up to 5 pre-specified dose levels of BAL101553, the starting dose will be 4 mg per day.

The overall sample size for the trial is not fixed. It depends on the number of dose levels being tested.

2.4 Dose escalation

Five patients will be enrolled at each dose level to ensure 3 evaluable patients at the end of the toxicity evaluation period. Accrual to the next dosing level will not start until a minimum of 10 weeks after the final patient is accrued to the lower dosing level. Dose escalation rules follow a 3+3 design in principle.

- If less than 1/3 of evaluable patients (i.e. 0/3, 0/4, 0/5, 1/4, or 1/5) in a cohort experience DLT, then a new cohort will be treated at the next higher dose level.
- If one of three evaluable patients in a cohort experiences DLT, then three additional patients will be treated at the same dose level.
- If 2-3 patients in a cohort or ≥3 in case of 2 cohorts treated at the dose level experience DLT, then the MTD will have been exceeded, and no further dose escalation will occur. The previous dose level will be considered as the MTD.
- If only three evaluable patients were treated at a dose level under consideration as the MTD, then three additional patients will be accrued. If no more than two of the six patients at that dose level experience a DLT, then that dose level will be confirmed as the MTD. If three or more patients in that cohort experience DLT, then the previous dose level will be studied in the same fashion.

2.4.1 Assessments

Table 1 presents a summary of the schedule of assessments performed from Baseline through the Follow-up visit (Cross-references in the footnotes are to protocol sections).

Table 1 Schedule of assessments

	Baseline	Day 1	Weeks 1-6	Weekly	Day 22	Off Treatment (within 7 days)	30 Day Follow-Up
BAL101553			6				
Corticosteroid Dose Evaluation	1					8	
Prior and Concomitant Medications	1,16			3		8	
AE Evaluation	1			3		8	5,12
Brain MRI	1					8	
H&P/Neuro Exam	1				7	8	
KPS	1				7	8	
Mini-Mental State Examination (MMSE®)		20		3, 20			
Vital Signs	1,4			3,4,14		4,8	
CBC, Diff, Platelets	1			2,3		2,8	
Serum Chemistry	1,10			3,10,13,15		8,10	
Cardiac troponin	1			3,15		8	
Echocardiography, cardiac MRI or MUGA	1						
APTT or PTT and INR	1						
Serum Pregnancy Test	9						
ECG	1			17		(8, 17)	
Archived Tumor Tissue	11						
Blood Samples for PK Analyses		18			18		
Study drug dispensing		19		3, 19			

1. All baseline measurements must be done after obtaining written informed consent and must be performed within 14 calendar days prior to first treatment administration except for the baseline MRI, which may be obtained within 21 days prior to first study drug administration, and the corticosteroid dose evaluation, which should be obtained within 5 days prior to the baseline MRI.
2. If ANC < 1500 or platelets < 100,000, CBCs/differentials will be repeated twice a week until counts are recovered (ANC ≥ 1500 or platelets ≥ 100,000) per protocol. If counts are recovered (ANC ≥ 1500 or platelets ≥ 100,000) on day of scheduled drawing, do not repeat until next scheduled protocol study visit.
3. ±1day
4. Including blood pressure, respiratory rate, heart rate, temperature, weight, height. Weight and height are required at baseline only.
5. Adverse events must be followed for at least 30 days from last dose of BAL101553.
6. BAL101553 is administered orally every day during radiation therapy (see Protocol - Section 4.4.1). Patients are required to keep a capsule diary (see Protocol - Appendix I).
7. ±3 days
8. Evaluations are to be performed within the 7 days following the off-treatment date, unless indicated. Evaluations that do not need to be repeated include: MRI if performed within the 14 days prior to the off-treatment date; H&P/neuro, KPS, or labs if performed within the 5 days prior to the off-treatment date.
9. For women of child-bearing potential. Pregnancy testing must be performed within 72 hours prior to first study drug administration.
10. Including albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, magnesium, phosphorus, potassium, SGOT, SGPT, sodium.
11. Unstained slides or tumor blocks from initial resection at diagnosis of glioblastoma, dependent on availability (Protocol - Section 9.5.2).
12. Within +14 days. May be performed at the off-treatment visit if at least 30 days from last dose of BAL101553.

13. A serum sodium level of < 130 mmol/L (CTCAE Grade 3) that is symptomatic or not reversible within 3 days, or that re-occurs upon study drug continuation or re-initiation at the same dose, is a DLT. Under these circumstances, study treatment must be discontinued temporarily or permanently, depending on the improvement/normalization of sodium levels (see Protocol – Section 5.1). Serum sodium testing must be repeated twice a week until recovered to ≥ 130 mmol/L.
14. If SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, initiate intervention, Protocol - Section 4.6.2. Patients with SBP ≥ 160 mmHg or DBP ≥ 100 mmHg must take BP daily until < 160 mmHg AND DBP < 100 mmHg. Patients should record BP readings in the pill diary (Protocol - Appendix I)
15. Perform weekly during RT+BAL101553 treatment (Days 8, 15, 22, 29, 36, 43); after RT is complete, perform every other week (Day 57 and off treatment).
16. Record all medications taken within 14 days prior to baseline (screening) visit.
17. ECG assessments to be done pre-dose and 2 h (± 30 mins) post-BAL101553 administration on Days 1, 8, 15, 22, 29 and 36 (±1day from Day 8 onwards). A final ECG will be taken within 7 days after the final dose of BAL101553. Patients with any abnormal ECG readings during the study will have an additional ECG performed at the end of the 10-week study period.
18. PK samples will be collected on Days 1 and 22: pre-dose and 0.5 h, 1 h, 2 h (up to 3 h), 4 h, 6 h (± 15 mins) and 24 h (± 1 h) post-dose (see Protocol - Section 9.5.1).
19. New study drug will be dispensed to patients at study visits at weekly intervals. All safety parameters (including laboratory safety parameters and MMSE®) applicable for assessing the ability for a patient to continue receiving study medication must be reviewed at any study visit prior to dispensing new study medication (see Protocol – Section 5.2).
20. The MMSE®,[21] will be performed predose on Day 1 (=baseline) and weekly during RT+BAL101553 treatment when no Neuro Exam is planned (Days 8, 15, 29, 36, 43). Based on the MMSE® Score, a Neuro Exam will be scheduled within 1 calendar day if both of the following conditions apply: score < 26 and decline against baseline > 3; see Protocol - Section 5.2.2.

Patients will be followed until death. Patients will only be off study at the time of death. Patients will be followed every two months for progression, for up to one year from the off-treatment date. All patients will be followed for survival every 2 months for the first 2 years; after 2 years, patients will be followed every 6 months until death.

2.4.2 Planned sample size

The overall sample size for the trial is not fixed. It depends on the number of dose levels being tested.

The 3+3 design does not require sample size specification; the escalation is continued until the maximum administered dose (i.e., a dose with an unacceptable number of DLT) is observed. In total, 26 patients are included in the study.

2.5 Interim analyses

No interim analyses are planned.

3 ANALYSIS POPULATIONS

3.1 Full analysis population (FAP)

The FAP includes all patients who received at least one partial or complete dose of study drug, based on the intent-to-treat principle. The FAP will be used for analyzing efficacy.

Considering that all patients were treated, all analyses will be performed on the safety population (see 3.2).

3.2 Safety population

All patients who received at least one full or partial dose of BAL101553 and had at least one post-baseline safety assessment must be included in the safety analysis populations. The safety analysis population will be used for all safety related analyses (AEs, vital signs, laboratory data, etc.).

Patients will be primarily analyzed according to their originally-assigned dose level.

3.3 PK population

All patients who received at least one full dose of BAL101553 must be included in the PK analysis population.

Protocol deviations that have an impact on the calculation or interpretation of concentrations or PK parameters will be listed in the PK report.

3.4 Maximum tolerated dose-determining population

The MTD-determining population includes all patients from the safety set who meet the following minimum criteria:

- Received at least one dose of BAL101553 and has experienced a DLT;
- Have completed ≥80% of their expected dose of BAL101553 for the 6 weeks of combined treatment and 4 weeks of rest (10 weeks total).

Patients who do not meet these minimum evaluation requirements will be regarded as ineligible for the MTD-determining population. These patients will be included in the safety population but will be excluded from the MTD-determining population.

4 STATISTICAL CONSIDERATIONS AND ANALYSIS

4.1 Derived variables

The following derived variables will be applied throughout the study:

- Baseline is defined as the last available assessment prior to first study treatment administration (including unscheduled assessments).
- Adverse event duration (in days, hours or fractions of hours) will be calculated as:
  - (<event end date.time> minus <event onset date.time>) in days or hours.

  If only the date is collected:
  - ((<event end date> minus <event onset date>) + 1) in days.
- The following algorithm will be used for the study day determination:
  - Day 1 = Day of first study drug administration (i.e., Day 1). The day before Day 1 is Day −1.
  - Prior to Day 1 the algorithm is (<visit/examination date> minus <date of first study drug administration>)
  - Day 1 and subsequent days = (<visit/examination date> minus <date of first study drug administration>) + 1.

- Duration of exposure (in days) will be calculated as: (<date of last study drug administration> minus <date of first study drug administration>) + 1.
- The progression status will be as reported in the case report form (CRF).

4.2 Handling of missing data and/or invalid data and outliers

4.2.1 Missing dates and times

Incomplete/partial dates will be replaced by derived variables and imputed using the following rules:

- If the day of the month is missing, it is imputed to be the 15th if not in the month of treatment. In the event that this leads to inconsistencies with other available data for the patient or if in the month of treatment, the imputation values will be handled case-by-case.
- If both the day and month are missing, they are imputed to be 30 June if not in the year of treatment. In the event that this leads to inconsistencies with other available data for the patient or if in the year of treatment, the imputation values will be handled case-by-case.
- Missing years will be left as missing.
- Missing time will be replaced by '00:00' for start times and '23:59' for end times if time is required.
- Missing minutes will be replaced by '00' for start times and '59' for end times if time is required.

4.2.2 Pharmacokinetic data

Treatment of outliers

Individual concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of the available documentation. Any such exclusion will be outlined in the PK report.
Entire individual treatment profiles for a subject may be excluded following review of the available documentation. However, results of analysis with and without the excluded profiles may be presented in the PK report. Any such exclusion will be clearly listed in the PK report along with justification for exclusion.

Non-quantifiable concentrations

All concentration values reported as no results (not collected or not determined) values will be treated as missing. For the calculation of concentration summaries, all concentrations below the quantifiable limit (BLQ) will be treated as 0.
For the purpose of calculating PK parameters and plotting mean and individual concentration time profiles, BLQ values will be treated as zero prior to the first measurable concentration. After the first measurable concentration, subsequent BLQ values will be treated as missing.

5 STATISTICAL PLAN AND METHODS

The statistical analysis will be performed using the software package SAS version 9.4 or higher (SAS Institute Inc., Cary, NC 27513, USA). All individual patient data, and results of statistical analyses, will be presented in individual patient data listings and statistical summary tables.

In general, continuous variables will be summarized using the following standard descriptive summary statistics: mean, standard deviation, median, minimum, maximum and number of observations. Categorical data will be described using frequency and percentage. Shift tables will be provided, where appropriate. One additional decimal point will be used for mean, median, Q1, Q3, and two additional decimal points will be used for standard deviation. Percentages will be rounded to one decimal place or more if most results are close to 0 or 100.

Any changes in the planned statistical methods will be documented in the clinical study report.

The following international dictionaries will be used for medical coding:

- Medical History events: MedDRA (version 24.0 or later)
- Adverse events: MedDRA (version 24.0 or later)
- Prior cancer related surgery (MedDRA Version 24.0 or later)
- Prior and concomitant procedures (MedDRA Version 24.0 or later)

Concentration-time profiles of BAL0101553 and BAL27862 will be analyzed by noncompartmental methods and/or nonlinear least squares regression using Phoenix WinNonlin (Build 8.3 or higher; Certara, Princeton, New Jersey, USA). The PK analysis will be reported in a separate report.

5.1 Background characteristics

5.1.1 Patient disposition

Enrollment and disposition data will be presented for each patient in data listings, and summarized by frequency tables. A disposition of patients includes the number and percentage of patients for the following categories: patients who completed the study treatment, patients who discontinued study treatment early with reasons for discontinuation.

Inclusion and exclusion criteria violations and patient enrollment eligibility will be presented by dose level and patient in data listings.

5.1.2 Protocol deviations

Protocol deviations reported during the course of the study will be listed.

Reported protocol deviations will be reviewed prior to database lock.

5.1.3 Demographic and baseline characteristics

Demographic and baseline characteristics of the safety population, including age at baseline, gender, race, ethnicity, height, weight, and disease characteristics, will be summarized by dose level using descriptive statistics or frequency tables, as appropriate. Percentages will be based on the number of patients with available observations in the safety population.

Demographic information and baseline characteristics will be presented in data listings sorted by dose level and patient.

5.1.4 Medical history

Diseases present at baseline as well as previous surgeries will be presented in data listings sorted by dose level and patient.

Medical history data will be summarized by dose level, system organ class (SOC), and preferred term (PT) using the safety population. Prior surgeries characteristics will also be summarized by dose level for the safety population.

5.2 Efficacy analysis

5.2.1 Overall survival

OS is defined as the time from Day 1 dosing to the date of death. Patients who have not died at study closure will be censored at the time of last known alive.

OS will be summarized for the safety population overall. The median time to death, as well as 25^{th} and 75^{th} percentiles, will be determined by Kaplan-Meier method. Its 95% CI will be performed using the Brookmeyer-Crowley method. The associated survival curve will be displayed.

OS will be listed by dose level and patient.

5.2.2 Progression-free survival

PFS is the interval between Day 1 dosing and the earliest date of progression or death due to any cause in the absence of progression. Patients who have not progressed or died at study closure will be censored at the time of their last assessment without progression.

If a patient has no post-baseline progression assessment, the PFS will be censored to 0 days.

PFS will be summarized for the safety population overall. Same statistics and curves than for OS will be displayed.

PFS will be listed by dose level and patient.

5.3 Pharmacokinetic analysis

Individual subject plasma concentration-time curves will be analyzed by noncompartmental methods. PK parameters will be presented as listings and descriptive summary statistics by dose groups and PK days. Individual and mean cohort plots of

concentration versus time will be constructed. Dose proportionality will be evaluated using the power model.

Pharmacokinetic parameters and variables will be calculated for BAL101553 (if applicable) and BAL27862 according to standard equations using actual sampling times if available.

Following administration, C_{max} and T_{max} will be obtained directly from the experimental observations. If multiple maxima occur at equal concentrations, the first temporal value will be taken.

AUC will be calculated using the linear up/log down trapezoidal rule, using actual elapsed time since the start of oral administration.

The number of data points included in the regression for determination of λz and t½ after single-dose will be determined by visual inspection, but a minimum of 3 data points in the terminal phase, excluding C_{max}, will be required to estimate λz. The λz values (and consequently t½, CL/F, Vd/F and AUC_{inf}) will be considered unreliable estimates if the time period over which an individual λz was estimated is less than twice the resultant t½ or if the adjusted coefficient of determination 'Rsq' is less than or equal to 0.75.
The proportion of AUC_{inf} due to extrapolation (AUC_{extrap}) will also be calculated and expressed as a percentage. The value of AUC_{extrap} should be less than or equal to 20% for AUC_{inf} to be considered to be well estimated. If AUC_{extrap} is higher than 20%, then the values of AUC_{inf}, CL/F, and Vd/F will be considered unreliable and therefore excluded from the summaries.

5.4 Safety analysis

Safety assessments will be conducted throughout the entire study period. Analyses will be performed using safety population, unless otherwise specified.

The safety evaluations will include analyses of adverse events, laboratory assessments (hematology, biochemistry, cardiac troponin, and coagulation), ECG, magnetic resonance imaging (MRI) scan, and vital signs.

5.4.1 Dose-limiting toxicity

The DLTs will be listed by dose level and patient.

5.4.2 Treatment exposure and radiation therapy

The duration (in days) of BAL101553 exposure, the actual dose received, and treatment compliance (as collected in the CRF), will be listed by patient and summarized using descriptive statistics by dose level.

Any other treatment exposure information will also be included in the listing.

Study drug dose interruptions and reductions will be listed by patient.

The duration (in days) of radiation therapy, the actual dose, and percentage (as collected in the CRF) received will be listed by patient and summarized using descriptive statistics by dose level.

Any other radiation therapy information will also be included in the listing.

5.4.3 Adverse events

Treatment-emergent events are defined as all events occurring after BAL101553 treatment begins. Any adverse event starting prior to the first study drug administration will be reported as medical history. The relationship of an AE to study drug and RT is recorded as unrelated, unlikely, possible, probable, or definite.

For analysis purposes, 'related to BAL101553' AEs will be those reported as possible, probable, definite, or those for which the relationship is unknown.

Adverse events will be presented in data listings including dose level, patient, dates/times, study day of event, MedDRA SOC, PT, duration of the event, seriousness, CTCAE grade, intensity, drug adjustment, treatment taken, relationship to study drug, relationship to RT, and outcome.

An overview table (including only treatment-emergent AEs) will also be presented with the number (and percentage) of patients and number of events with:

- Any AE
- Related to BAL101553 AEs
- CTCAE grade 3/4 AEs
- CTCAE grade 3/4 related AEs
- SAEs
- Related SAEs
- AEs leading to dose modifications (i.e., dose reduced or dose interrupted)
- Related AEs leading to dose modifications (i.e., dose reduced or dose interrupted)
- AEs leading to study drug discontinuation
- Related AEs leading to study drug discontinuation
- AEs leading to death
- Related AEs leading to death.

This table will be displayed by dose level.

All treatment-emergent AEs and treatment-emergent AEs related to treatment will be summarized by incidence rate tables broken down by:

- SOC and PT.
- SOC, PT, and worst CTCAE grade.
- SOC, PT, and drug relationship.

Serious treatment-emergent AEs, treatment-emergent AEs leading to dose modifications, leading to study drug discontinuation, or leading to death will be also summarized by SOC and PT. The same analyses will be repeated for related AEs.

5.4.4 Laboratory evaluation

The laboratory tests for safety analyses comprise the following:

- Hematology: Hemoglobin, Platelet count, White blood cell count, Neutrophil count, Lymphocyte count,
- Serum biochemistry: Sodium, Potassium, Creatinine, Albumin, Alkaline phosphatase, Total and direct bilirubin, Aspartate amino transferase, Alanine amino transferase, Phosphate (inorganic phosphorus), Calcium, Magnesium.
- Cardiac troponin: Cardiac Troponin I, Cardiac Troponin T
- Coagulation: International normalized ratio, Partial Prothrombin Time and activated Partial Thromboplastin Time.

Laboratory values will be converted into SI units and the severity grade determined based on CTCAE.

Descriptive statistics for each laboratory analyte at each assessment time will be tabulated by dose level. The change from baseline will also be summarized by dose level.

An analysis of individual patient changes by dose level will be presented using shift tables showing the change from CTCAE grade/intensity at baseline to the worst CTCAE grade/intensity (including unscheduled assessments) during the study.

The laboratory parameters will be presented in data listings sorted by dose level, patient, study day, study time, and analyte. Out-of-range values will be flagged with h (high) or l (low).

5.4.5 Vital signs

Summary statistics by dose level and scheduled time point will be presented for each vital sign. The change from baseline will also be presented.

The mean maximum change from baseline (the average of the maximum change between baseline and all timepoints post baseline) will also be presented.

The number of patients with values outside marked reference ranges will also be tabulated by dose level and scheduled time point.

The vital signs marked reference ranges are:

- Diastolic blood pressure: < 60 mmHg or > 100 mmHg.
- Systolic blood pressure: < 80 mmHg or > 180 mmHg.
- Pulse: < 40 beats/min or > 120 beats/min.
- Temperature: < 36.0 degrees Celsius or > 38.5 degrees Celsius.

Vital sign assessments will be presented for each patient in a data listing by dose level.

5.4.6 ECG results

The 12-lead ECG results (QTcF interval reported in the CRF) and changes from baseline will be summarized using standard descriptive statistics by dose level and scheduled time point.

ECG results will be presented for each patient in a data listing by dose level.

5.4.6.1 Outlier analysis

The number and percentage of patients with maximum on-treatment value of QTcF interval, categorized as ≤ 450 msec, > 450 msec and ≤ 480 msec, > 480 msec and ≤ 500 msec, and > 500 msec, as well as maximum on-treatment change from baseline value of QT/QTc intervals, categorized as < 5 msec, ≥ 5 msec and < 10 msec, ≥ 10 msec and < 20 msec, ≥ 20 msec and < 30 msec, ≥ 30 msec and < 60 msec, and ≥ 60 msec will be tabulated based on scheduled and unscheduled 12-lead ECG measurements.

5.4.7 Physical examination

General physical examination assessments will be listed by dose level, patient, and study day.

5.4.8 Prior and concomitant medications

Medications and significant non-drug therapies prior to and after first administration of the study drug will be listed by dose level and patient.

5.4.9 MRI Scan

MRI Scan results will be presented for each patient in a data listing by dose level.

5.4.10 Neurological examination

Neurological and Mini-Mental State examination results will be presented for each patient in a data listing by dose level.

6 CHANGES FROM THE PLANNED ANALYSIS IN STUDY PROTOCOL

OS and PFS will use the “Day1 dosing” date instead of “initial diagnosis” date as starting point. For OS, event rate will not be estimated, only median and quartiles will be estimated using Kaplan-Meier method.

Only the number and percentage of patients who experienced grade 3 or above toxicity will be displayed, no 95% CI confidence interval will be estimated.