NOVARTIS

Clinical Development

LTT462

Oncology Clinical Trial Protocol CLTT462X2101 / NCT02711345

A phase I dose finding study of oral LTT462 in adult patients with advanced solid tumors harboring MAPK pathway alterations

Statistical Analysis Plan (SAP)

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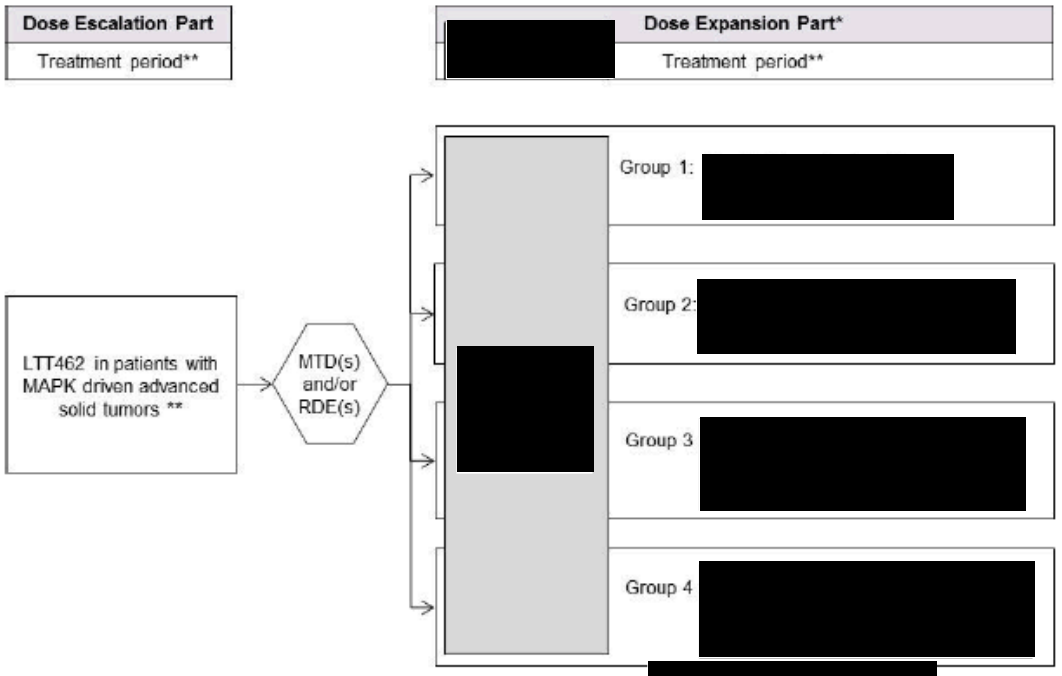
1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CLTT462X2101 that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the TFL shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document.

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., MTD/RDE declaration, IB updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 Study design



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[redacted]

[redacted]

1.2 Study objectives and endpoints

Table 1-1 Primary and secondary objectives

Objective	Endpoint
Primary	
To characterize safety and tolerability of LTT462 and identify a recommended dose and regimen for future studies in adult patients with advanced solid tumors harboring MAPK pathway alterations.	**Safety:** Incidence and severity of adverse events (AEs) and serious AEs (SAEs), including changes in laboratory values, vital signs, and ECGs. Incidence and nature of DLTs (dose escalation only) **Tolerability:** Dose interruptions, reductions, and dose intensity
Secondary	
To evaluate the preliminary anti-tumor activity of LTT462	**For both parts:** Overall response rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR), and Progression Free Survival (PFS) as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [redacted]
To evaluate the pharmacokinetic (PK) profile of LTT462	Plasma concentrations and derived PK parameters of LTT462
To assess the pharmacodynamic (PD) effect of LTT462	Changes from baseline of the PD marker DUSP6 in tumor tissue and in blood.

2 Statistical Methods

2.1 Data analysis general information

Study data will be analyzed by Novartis personnel and/or designated CRO(s) using R . The most updated SAS® version available in the programming environment PK parameters will be calculated using non-compartmental methods available

The primary clinical study report (CSR), if final DBL has not occurred, will include all patients' data reported during the dose escalation and dose expansion parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. The primary CSR will include all outputs planned within the TFL shells document. A final (or closeout) CSR will be produced once all patients have discontinued the study.

Data from participating centers will be combined, so that an adequate number of patients will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) and pharmacodynamics (PD) measurements using descriptive statistics (n, mean, standard

deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

Both pre and post intra-patient dose escalation data will be listed and summarized together under the one dose level/treatment group.

Cohorts of patients treated during the dose escalation part with the same dose levels, regimen [redacted] will be pooled into one single *treatment group*. [redacted] Below an illustration of the grouping, there will be no difference between safety and efficacy layout of outputs (more details are included in the TFL shells document).

Table 2-1 General display of information

	Dose Escalation				[redacted]
	Treat A N=xx n (%)	Treat B N=xx n (%)	Treat C N=xx n (%)	All patients N=xx n (%)	
variable	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
variable	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
variable	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	

If during the course of the study different groups of interest are identified, the SAP will be updated accordingly.

2.2 General definitions

Study drug and study treatment

Study drug and study treatment refer to LTT462 and are used interchangeable.

Date of first/last administration of study drug and study treatment

The date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of study treatment LTT462 was administered and recorded on the Dosage Administration Record panel. For the sake of simplicity, the date of first (last) administration of study treatment will also be referred as start (last) date of study treatment.

Study day

The study day for all assessments/onset of events will be calculated using the start date of study treatment as reference. For assessments/events occurring on or after the start date of study treatment, study day will be calculated as:

Study day (days) = Event date – Start date of study treatment + 1

Therefore, the first day of study treatment is study day 1.

For all assessment/onset of events occurring prior to the start of the study treatment, study day will be negative and will be calculated as:

Study day (days) = Event date – Start date of study treatment

On-treatment assessment/event

An on-treatment assessment/event is defined as any assessment/event in the time interval from the start date of LTT462 treatment [redacted] until the last date of LTT462 treatment + 30 days inclusive.

LTT462 dose interruption

Study drug dose interruption is defined as a "total daily dose" equal to zero, between the first and last non-zero doses, following a non-zero total daily dose. This applies to any regimen, in our case QD [redacted] and independently of the reason for interruptions.

LTT462 dose reduction

Time points at which the dose change flag is checked and the total daily dose is nonzero.

If the total daily dose at that time point is lower than the total daily dose at the time that the last non-zero dose was administered then the dose change is identified as a dose reduction.

2.3 Analysis sets

Full Analysis Set (FAS)

The FAS will be the default to be used for all efficacy analyses. Listings of raw data will use the FAS, unless otherwise noted. It includes all patients who received at least one dose of study drug (full or partial). Patients will be classified according to the planned (i.e., assigned) treatment (dose level, regimen, [redacted]).

Safety Set

The safety set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship. It includes all patients who received at least one dose (full or partial) of study treatment. The statement that a patient did not experience an adverse event constitutes a valid safety assessment. Patients will be analyzed according to the treatment received, where treatment received is defined as:

- The treatment assigned, if it was received at least once, or
- The first study treatment received, if the treatment assigned was never received.

Dose-determining Set

The DDS consists of all patients from the safety set in the dose escalation part of the trial who either meet the following minimum exposure criterion and have sufficient safety evaluations

during the first 28 days of dosing or discontinue earlier due to a DLT during the first 28 days of dosing. This constitutes an evaluable patient for the determination of MTD. Patients in the DDS will be identified prior to each dose escalation meeting and will be confirmed prior to database lock.

In this study, if data on AEs, vital signs, Labs, and dose administration is collected at least at study visits C1D1, C1D8 and C1D15, patient is considered as having sufficient safety evaluations. The statement that a patient did not experience an adverse event constitutes a valid safety assessment.

A patient is considered to have met the minimum exposure requirement if they have received at least 75% of the planned doses of each of the assigned combination drugs during the first cycle (the first 28 days of dosing). For all regimens proposed this equates to at least 21 of the planned 28 doses LTT462.

Patients who do not experience a DLT during the first 28 days of dosing are considered to have sufficient safety evaluations if they have been observed for 28 days or more following the first dose, and are considered by both Novartis and Investigators (at the dose escalation meetings) to have enough safety data to conclude that a DLT did not occur.

PK analysis set for the treatment period

The Pharmacokinetic Analysis Set (PAS) includes all patients who have at least one PK blood sample providing measurable LTT462 and who satisfy the bullets below:

- received at least one dose of LTT462,
- patient provided at least one primary PK parameters,
- patient did not vomit within 4 hr of dose administration,

[redacted]

The PAS will be used for summaries of PK data (tables and figures) as well as for listings of derived parameters.

2.3.1 Exclusion from analysis sets

In general, a patient must have provided written informed consent before inclusion into any analysis set, as specified in section 5.2 of the study protocol.

Table 2-2 Reasons for excluding a patient from an analysis set

Analysis set	Deviation
Full analysis	Patient did not receive at least one dose of LTT462
Safety	Patient did not receive at least one dose of LTT462.
	Patient without at least one post-baseline safety assessment.

Analysis set	Deviation
Dose-determining	Patient did not experience a DLT, however, the requirement of a minimum exposure to the planned study treatment was not met.
PK analysis,	If any of the conditions detailed above are violated, patient will be exclude from PAS

2.4 Subgroup analyses

None identified to date.

2.5 Patient demographics and other baseline characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the FAS.

2.5.1 Basic demographic and background data

Demographic data including age, age categories (<65, ≥65 years), sex, race, ethnicity, height, weight, LVEF, and ECOG performance status at baseline will be listed and summarized.

2.5.2 Medical History

Medical history and current medical conditions will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting. Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms will be available as listing.

2.5.3 Prior antineoplastic therapy

The number (%) of patients who received prior anti-neoplastic medications will be summarized and listed.

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), therapy type at last medication, setting at last medication, best response at last medication (defined to be the best response during the last treatment regimens recorded), time (in months) from (end of) last medication to Progression,. The last medication is defined based on the last end date of all prior regimen components. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

All Prior anti-neoplastic therapies (medications, surgery and radiotherapy) will be available at a patient level (listing).

2.5.4 Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include primary site of cancer, details of tumor histology/cytology, histological grade, stage at initial diagnosis, stage at time of study entry time (in months) from initial diagnosis of primary site to start of study treatment, time (in months) since most recent recurrence/relapse or progression to start of

study treatment, time (in months) from initial diagnosis of primary site to first recurrence/relapse or progression, current stage of cancer, current extent of disease (metastatic sites), and type of lesions (target and non-target lesions) at baseline.

2.6 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated:

- Number (%) of patients who are still on-treatment,
- Number (%) of patients who discontinued treatment,
- Primary reasons for study treatment discontinuation,
- Number (%) of patients who are still on study,
- Number (%) of patients who discontinued from study,
- Primary reasons for study discontinuation.

2.7 Protocol deviations

The FAS will be used for the protocol deviation listing. The full list of protocol deviations is documented in the Study Specification Document (SSD).

2.8 Treatments (study treatment, concomitant therapies, compliance)

Unless otherwise noted, the safety set will be used for all summaries and listings described in this section.

2.8.1 Study treatment

Last date of exposure to LTT462 is the last date of study treatment.

Study treatment will be summarized in terms of duration of exposure to study treatment, cumulative/average daily study drug dose, study drug intensity (DI).

- Duration of exposure (days): last date of exposure to study treatment − first date of study treatment + 1 (periods of interruption are not excluded)
- Cumulative dose (mg): sum of all total daily doses of study drug taken by a patient
- Cumulative planned dose (*mg*): sum of all doses of study drug that was intended to have been taken during the treated period by a patient
- DI (mg/day): cumulative dose (mg)／number of doses scheduled per protocol during treatment period
- Relative DI: Cumulative dose (mg)／Cumulative planned dose (mg)

The duration of exposure to study treatment will also be summarized following the categories: <4, <=4, <=8, <=12, <=16, <=24 weeks.

Relative RDI will also be summarized following the categories: <0.5, 0.5-<0.75, 0.75-<0.9, 0.9-<1.1, ≥1.1 for each study drug.

A listing of patient's dose administration records will be presented.

2.8.2 Concomitant therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Any concomitant therapies starting prior to or after the start of study treatment will be available at a patient level (listing).

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 2.11.1 Adverse events). No imputation will be performed for concomitant medication end dates.

2.9 Analysis of the primary variables

2.9.1 Primary variables

The primary endpoints defined to evaluate the safety of LTT462 are incidence and severity of AEs/SAEs, changes in hematology and chemistry laboratory values, changes in vital signs, changes in ECG, and incidence and nature of DLTs (dose escalation only). Tolerability will be evaluated in terms of dose interruptions, dose reductions, and dose intensity.

2.9.2 Statistical model and method of analysis

DLTs (in the dose escalation part) will be analyzed using a BHLRM. The incidence of DLTs will be summarized by system organ class (SOC) and preferred term. The DDS will be used to analyze DLTs. [redacted]

Statistical analysis of endpoints other than incidence of DLTs will be descriptive, based on the safety analysis set, no hypotheses or models will be considered. Details of analysis are provided in the safety and tolerability sections, respectively. Descriptive statistics will be provided on:

- The incidence by patients of AEs**,** independent of relationship to study drug, and also considering severity
- The incidence by patient of serious AE, independent of relationship to study drug
- Changes from baseline to worst post-baseline hematology and chemistry laboratory values
- Changes from baseline to worst post-baseline values of ECG parameters
- Changes in vital signs from baseline to worst post-baseline values
- Summary of dose intensity, and number and percentage of dose interruptions and reductions

2.9.2.1 Dose limiting toxicities (dose escalation)

Statistical model

The dose escalation will be guided by a BHLRM based on the first Cycle DLT data of the study treatment. This model estimates the relationship between dose and the probability of a patient experiencing a DLT following a QD regimen [redacted]

[redacted]

Dose recommendation

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels will be obtained for each stratum. Dose recommendation will be based on posterior summaries including the mean, median, standard deviation, 95%-credible interval, and the probability that the true DLT rate for each dose lies in one of the following categories:

- [0,16%) under-dosing
- [16%,33%) targeted toxicity
- [33%,100%] excessive toxicity

Dose recommendation will also be guided by the EWOC principle, which mandates the dose for the next cohort to have less than 25% chance of excessive toxicity. The final estimate of the MTD/recommended dose for expansion will also satisfy this condition.

Reports

The dose determining set will be used in the following outputs:

- A heatmap (in-text) of the posterior distribution of DLT rates,
- a listing (CSR appendix 16.1.9) of inferential results from the BLRM at the time of the MTD declaration,
- a summary of the DLTs with onset during the first cycle of treatment (dose escalation part only) by primary system organ class, preferred term, and treatment group
- a listing of patients with DLTs reported during the first cycle of treatment.

2.9.2.2 Analysis of other primary Endpoints

Refer to sections 2.11 and 2.12

2.10 Analysis of efficacy variable(s)

Tumor response will be determined locally according to RECIST v1.1 (Appendix 1.1 of the study protocol), as per local investigators' assessment. The FAS will be used for all efficacy analyses.

Dose escalation part

For the dose escalation part, the best overall response (BOR) and individual lesions, DOR (if applicable) and the PFS time will be presented for each patient in a listing. PFS, ORR and DCR will be summarized by treatment group.

2.10.1 Confidence intervals for ORR

An exact binomial confidence interval (implemented using the SAS procedure FREQ with the EXACT statement for one-way tables) will be calculated (Clopper CJ, 1934). [redacted]

2.11 Analysis of safety variables

The assessment of safety is based on the type and frequency of Adverse Events (AEs) as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria for Adverse Events (CTCAE version 4.03) grading limits or normal ranges as appropriate). Other safety data include ECOG performance status, electrocardiogram and vital signs.

The Safety set will be used for summaries and listings of safety data with the exception of dose limiting toxicities (DLTs) for which the DDS will be used.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of LTT462,
2. On-treatment period: from day of first dose of LTT462 to 30 days after last dose of study medication,
3. Post-treatment period: starting at Day 31 after last dose of LTT462.

Safety summary tables described in the following sections will include assessments collected during the treatment period, unless otherwise stated.

2.11.1 Adverse events

Data handling

AEs will be coded and graded using the latest version of MedDRA and CTCAE, respectively, available at the time of reporting. If CTCAE grading does not exist for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE grade 5 (death) will not be used in this study. Death information will be collected during treatment, safety follow up, and post-treatment follow up .

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors, should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

A patient with multiple CTCAE grades for an AE will be summarized under the maximum grade recorded for the event. A subject with multiple occurrences of an AE is counted only once in the AE category (e.g. SOC, preferred term).

The incidence of a given AE is defined as the ratio of total number of patients experiencing the given AE at least once (defined by its preferred term [PT]) divided by the total number of patients at risk (i.e. part of the safety set). The incidence of AEs will be performed on treatment-emergent events only, i.e., AE that first occurs or worsens during treatment up to 30 days following the last treatment administration. The listing of adverse events will include all events reported during the study conduct.

Reports

The following AE summaries will be produced, including maximum CTC grade 3/ 4, in addition to the primary analyses:

- AEs regardless of study drug relationship
- AEs suspected to be study drug related
- AEs leading to discontinuation of study drug, regardless of study drug relationship
- AEs which are not SAEs regardless of study drug relationship
- All SAEs regardless of study drug relationship
- On-treatment deaths with cause of death by preferred term
- All deaths, with cause of death by primary system organ class and preferred term

A missing AE start date will be imputed using the following logic matrix described below.

Table 2-3 Imputation rules for a partially missing AE start date

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	No imputation	No imputation	No imputation	No imputation
AEY < TRTY	(D)	(C)	(C)	(C)
AEY = TRTY	(B)	(C)	(B)	(A)
AEY > TRTY	(E)	(A)	(A)	(A)

AEM: Month AE started; AEY: Year AE started
TRTM: Month treatment started; TRTY: Year treatment started

Table 2-2 is the legend to the logic matrix shown in Table 2-1 and details the relationship of AE start date to study treatment start date.

Table 2-4 Imputation legend and AE/treatment start date relationship

	AE start date relationship	Imputation
(A)	After treatment start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(B)	Uncertain	TRTSTD+1
(C)	Before treatment start	15MONYYYY
(D)	Before treatment start	01JULYYYY
(E)	After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

No imputation will be performed for AE end dates.

2.11.2 Laboratory data

Data handling

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on local laboratory normal ranges.

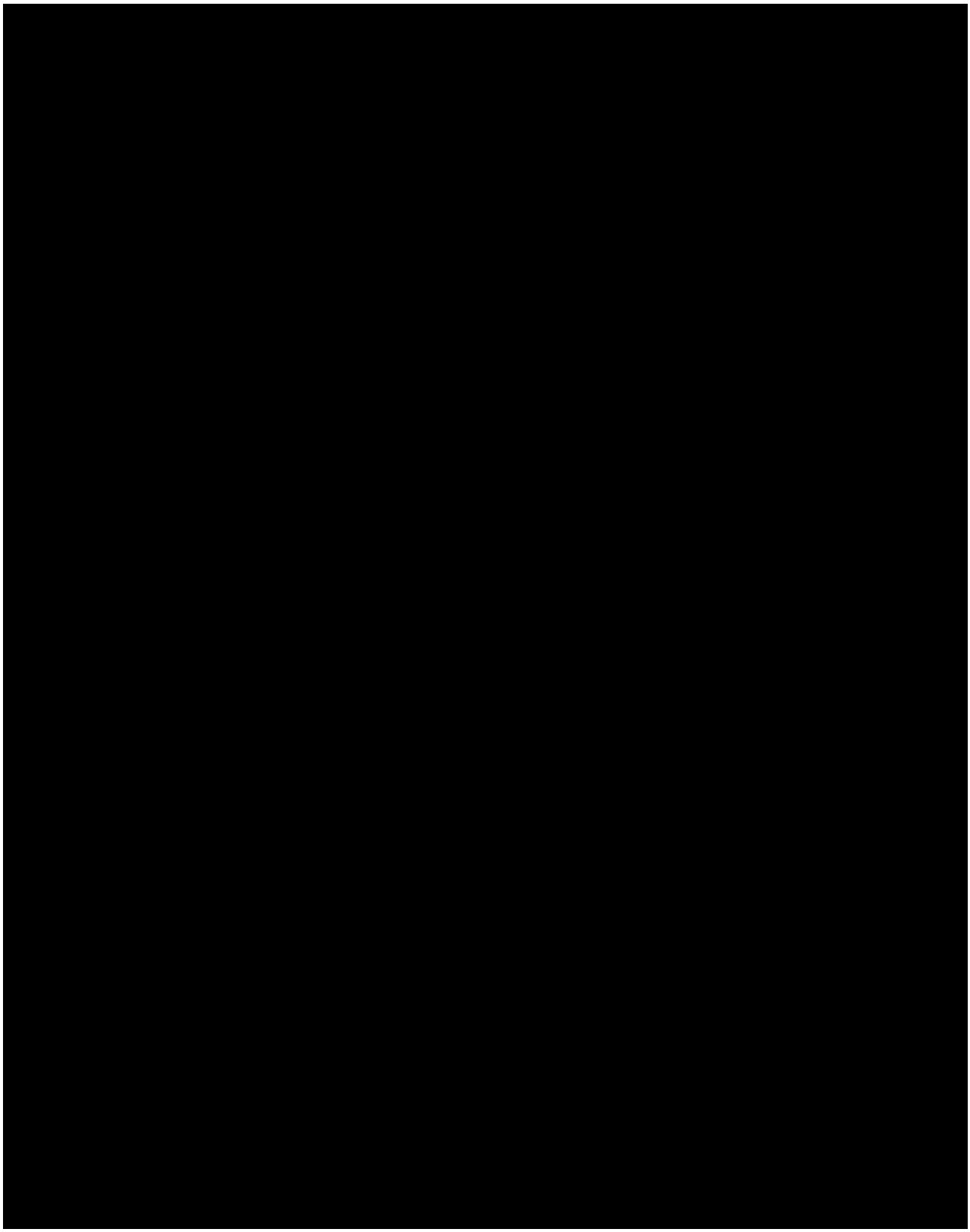
Laboratory parameters with CTCAE grading will follow the EASE Lab CTC grade derivations:

- Lab values will be analyzed using programmable numeric CTCAE criteria , therefore not considering clinical components (e.g., life-threatening consequences). It is therefore understood that AEs on lab toxicities might not correspond fully with lab toxicities on lab values

The new Novartis Oncology standard definitions of lab CTC grades (including direction of severity) are given in Appendix 6.3. Of note this is the current version of the EASE report, at the time of the CSR, the most updated version will be applied,

Data analysis

A listing of patients with abnormal laboratory values of CTCAE grade 3 or 4will be produced for the hematology and chemistry laboratory data.



2.11.3 Other safety data

2.11.3.1 Electrocardiograms

Data handling

- Unscheduled ECGs are included in the analysis of notable value.
- Triplicate 12 lead sequential readings will be performed at baseline and post-baseline for a patient at the given time points, refer to section 7.2.2.6.1 of the study protocol, all individual values are transferred, in which case, ECGs are averaged over the patient and then across patients for change from baseline analysis.
- No adjustment (in the variance) is made to account for different patients having differing number of ECGs being averaged at a given time point. (It is assumed that the scheduled assessments for each patient are the same and any deviations are sporadic and minor.)

Data Analysis

A listing of ECG intervals will be presented, by treatment group for the dose escalation part.

2.11.3.2 Vital signs

A listing of patients with abnormal vital signs will be provided.

2.12 Tolerability

Tolerability of study drug treatment will be assessed by summarizing the number and percentage of dose interruptions and dose reductions per patient, together with reasons for dose interruption and dose reductions. Dose intensity and relative dose intensity of LTT462 per patient will be summarized. For relative dose intensity, the number and proportion of patients

within the following categories will be presented: < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1.

2.13 Pharmacokinetic data

Pharmacokinetic parameters will be determined by non-compartmental method(s) using the pharmacokinetic profile of LTT462. PK parameters listed below will be derived and reported, when feasible.

Table 2-8 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Cmin	Observed concentration at the end of a dosing interval (taken directly before next administration)
CL/F	The total body clearance of drug from the plasma (volume x time-1)
Racc	Accumulation ratio calculated using AUCtau at steady state divided by AUCtau at Day 1
T1/2	Effective elimination half-life

2.13.1 Data handling principles

All concentrations below the lower limit of quantitation (LLOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters, unless otherwise stated under the Pharmacokinetic Analysis Set.

At the time of analysis, concentration data from patients may be removed from the estimation of certain PK parameters depending on the number of available blood samples, concomitant medications, vomiting, etc. Specific time points might be removed from the analysis, if technical issues with the sample are reported (e.g. sampling issues, missing information). These patients and concentration data points will be identified at the time of analysis.

2.13.2 Data analysis set

All pharmacokinetic data analyses and PK summary statistics will be based on PAS. Only PK blood samples with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses.

2.13.3 Basic tables, figures, and listing

Descriptive statistics will be presented for all pharmacokinetic parameters, as described below.

Table 2-9 Descriptive analysis

Parameters	Descriptive statistics
AUC(1), C_{min}, C_{max}, CL/F, accumulation ratio R_{acc}, $T_{1/2}$	Mean standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum. 90% CI for $R_{acc.}$
T_{max}	Median, minimum, and maximum.
<Other parameters>	None
(1) Includes AUC_{inf}, AUC_{tau}, AUC_{last} (or all AUC parameters) CV% = coefficient of variation (%) = sd/mean*100 CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100	

Zero concentrations will not be included in the geometric mean calculations. Tmax will be summarized in terms of median values and ranges. Missing concentrations or PK parameter values will not be imputed. A listing of derived PK parameters per patient will be produced by treatment group.

Arithmetic and geometric mean plasma concentration versus time profile plots will be generated for LTT462. Further graphical exploratory analyses (such as individual plasma concentration versus time) will be carried out if deemed appropriate.

2.13.4 Dose proportionality

Analysis of dose-proportionality will be performed if at least three doses of LTT462 are investigated.

Cmax and AUC will be used for dose proportionality analysis using the power model (Gough 1995). The power model empirical relationship between a PK parameter and dose is of the form

$$PK = Exp(\alpha)(dose)^{\beta},$$

where "PK" represents the PK parameter AUCinf or Cmax. For analysis, this equation is log-transformed (natural log), obtaining the equation

$$\log_e(PK) = \alpha + \beta \log_e(Dose),$$

The slope beta measures the dose-proportionality between Dose and the PK parameter

To test for dose proportionality, the confidence interval criteria for assessment of dose proportionality from Smith et al. (2000) will be used. The a *priori* acceptance range for the slope, according to Smith, is given by

$$1 + \frac{Ln(0.8)}{Ln(dose\_ratio)} < \beta < 1 + \frac{Ln(1.25)}{Ln(dose\_ratio)}$$

Where 1.25 and 0.8 are the critical *a priori* values suggested by regulatory authorities for any bioequivalence problem after a data log transformation, and "*dose_ratio*" is the ratio of the largest to the smallest dose. Dose proportionality can be claimed if the 90% confidence interval for the slope is entirely contained within this a *priori* range.

2.14 Biomarkers

As a project standard, Novartis Oncology BDM will analyze only biomarkers collected in the clinical database. [redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood / archival tumor samples / fresh tumor biopsies / fine needle aspirates due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of the samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

2.14.1 Outline of data analysis

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

2.14.2 Analysis data set

The Full Analysis Set will be used for all biomarker analysis. Assessment of association between biomarker and safety data will be conducted using the Safety Set.

2.14.3 General data handling

The last assessment before the first dose administration (pre-dose) will be used as baseline value. For assessments performed in tumor biopsies, fresh biopsy results will be used for baseline when both archived and fresh tumor samples are available. When more than one biomarker data are available for a subject at any time point, the mean of the replicate values will be used for all statistical analyses.

2.14.4 Dual specificity phosphatase 6 (DUSP6)

For assessment of PD effects of LTT462 in tumor, pre- and post- treatment tumor biopsies will be examined for expression of DUSP6. For assessment of PD effects in blood, levels of DUSP6 will be measured in samples isolated concomitantly with those collected for PK measurements.

2.14.4.1 Handling of [redacted] data

Percent Change in DUSP6 Expression is derived from the Relative Expression Ratio (RER), calculated according to the 'Comparative CT Method' described in Applied Biosystems User Bulletin #13 (2001) and consistent with the model described in (Pfaffl and Hageleit 2001). In this method, ΔCT is computed by subtracting the CT of a Reference Gene from the CT of DUSP6 for both Baseline and Post-Baseline Samples. RER is calculated by raising 2.0 to an exponent computed by subtracting the (ΔCT) of the Baseline Sample from (ΔCT) of the Post-Baseline Sample. RER is transformed by subtracting 1.0, such that expression increases and decreases are indicated when %Change is greater than or less than zero, respectively.

2.14.4.2 Deriving change from baseline in DUSP6 expression

Denoting the baseline (ΔCT) of one patient as **B** and the post-baseline as **PB**, then

- RER = 2^(B-PB)

% Change in expression relative to Baseline = **(RER -1)***100

2.14.4.3 Biomarker data reports

Table 2-10 Biomarker data reports

Type of sample (time point)	Biomarker	Biomarker assay	Table	Figure
Tumor [redacted]	DUSP6	[redacted]	- Summary of baseline and percentage change (absolute and fold) from baseline in [redacted] DUSP6 expression. (descriptive statistics include: mean, geometric mean, std, %CV, median, min-max) -	- Waterfall plot to depict the change from baseline in [redacted] DUSP6 expression annotated with the BOR - longitudinal plot of DUSP6 expression levels over time
Blood	DUSP6	[redacted]	- Summary of baseline and percentage change (absolute and fold) from baseline in [redacted] DUSP6 expression. (descriptive statistics include: mean, geometric mean, std, %CV, median, min-max)	- Waterfall plot to depict the change from baseline in [redacted] DUSP6 expression annotated with the BOR - longitudinal plot of DUSP6 expression levels over time

2.14.5 Advanced analysis methods

Additional analyses that may be performed after the completion of the final CSR will be documented in separate analysis reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in a separate analysis plan document and may be included in the CSR.

3 Interim analysis

No formal interim analyses are planned. However, the dose escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose escalation part, the next dose of LTT462 has to be chosen depending on the observed data. Details of this procedure and the process for communication with Investigators are provided in Section 6.2.3 of the study protocol.

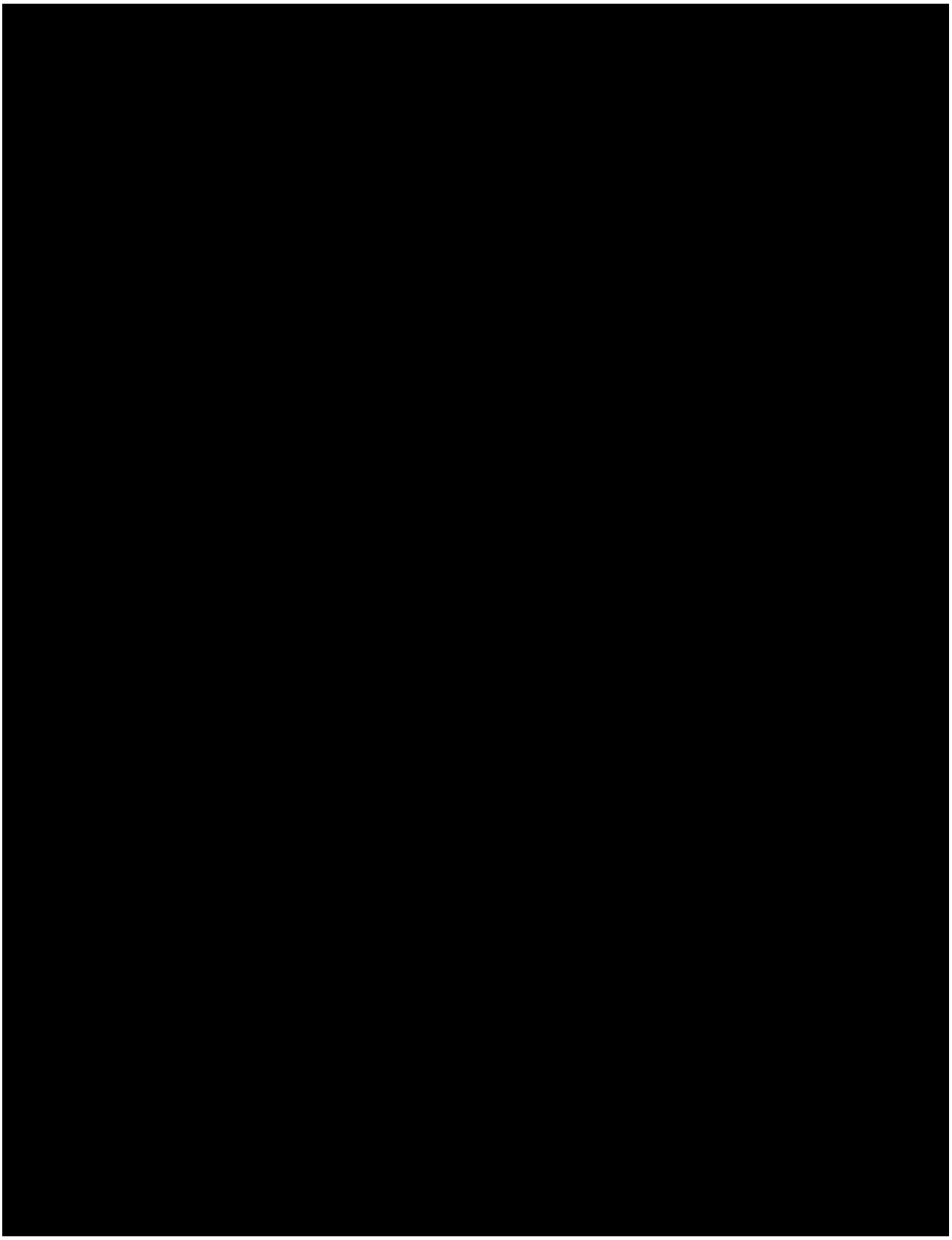
[redacted] Cumulative study data (including safety, tolerability, preliminary anti-tumor activity, PK, and PD) will be reviewed on an ongoing basis by Novartis and study investigators.

4 Sample size calculation

4.1 Dose-escalation part

Initially, cohorts of 1 to 3 evaluable patients will be enrolled in the dose-escalation part. Upon observation of specific toxicities, cohorts of 3 to 6 evaluable patients will be enrolled including at least six patients at the MTD/RDE level, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RDE for further elaboration of safety and pharmacokinetic parameters as required. At least 21 patients are expected to be treated in the dose escalation part, for the model to have reasonable operating characteristics relating to its MTD recommendation. In the event that a lower dose is recommended for the use in the dose expansion without identification of the MTD, then the sample size may be smaller than 21.

[redacted]



5 Changes in planned analysis

Changes to planned analyses will be documented in section 9.8.3 of the CSR..

6 Appendix

6.1 Baseline

Baseline is the last available and valid assessment performed or value measured before the first administration of LTT462, unless otherwise stated under the related assessment section. Baseline can be the day before first treatment administration or the same day as first treatment administration if a pre-dose assessment/value is available (e.g., PK samples, samples for biomarkers).

If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment will be considered as baseline only if it is actually performed before the first dose, as checked using both times.

If time is not recorded, a specific assessment performed the day of first dose administration will be considered as baseline if, according to protocol, it should be performed before the first dose.

Patients with no data on a particular parameter before the first treatment administration will have a missing baseline for this parameter.

6.2 Handling of missing and partial dates

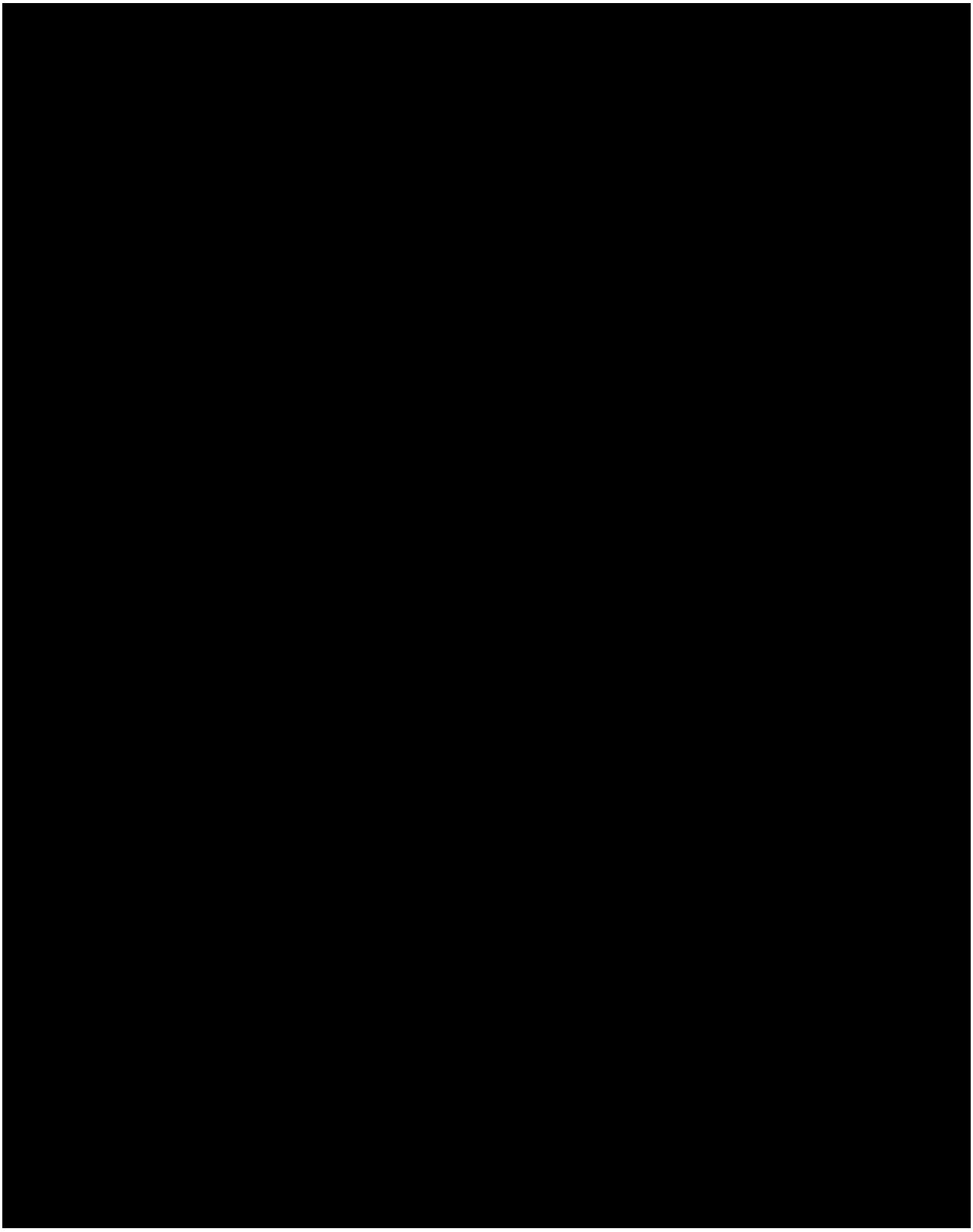
For patients not known to have died prior to the cut-off date:

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will be reported as continuing at the cut-off date. For these events, the end date will not be imputed.

For patients known to have died prior to or on the cut-off date:

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed to the date of death. For these events, the imputed end date will not appear in the listings.

If imputation of an end date is required for a specific analysis (e.g. a dose administration record with missing end date, or last date of study treatment is after the cut-off date), the end date will be imputed to the cut-off date in order to calculate e.g., the duration of exposure to study treatment. The imputed date will be displayed and flagged in the listings.



7 References

Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time, *Biometrics* 38, 29 - 41.