STATISTICAL ANALYSIS PLAN COVER LETTER

A Phase 2, Multicenter Study of Tesevatinib Monotherapy in Patients with Recurrent Glioblastoma

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
ADI	Actual dose intensity
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ATC	American Therapeutic Chemical (Classification)
BID	Twice daily
C1D1	Cycle 1 Day 1
CI	Confidence interval
CM	Concomitant medication
CNI	Calcineurin inhibitor
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
EOT	End of treatment
ICH	International Conference on Harmonisation
LR	Lack of response
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
KPS	Karnofsky Performance Scale
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
OS-9	Overall survival at 9 months
PD	Pharmacodynamics
PDI	Planned dose intensity
PFS	progression-free survival
PFS-6	progression-free survival at 6 months
PK	Pharmacokinetics
PR	Partial response
PT	Preferred Term
RANO	Response Assessment in Neuro-Oncology criteria
RDI	Relative dose intensity
RV	Residual volume
QD	Once daily
ORR	Overall response rate
QTcF	Corrected QT interval using Fridericia's formula
SAE	Serious adverse event

Abbreviation	Full Term
SAP	Statistical Analysis Plan
SOC	System Organ Class
STB	Stable
TEAE	Treatment-emergent adverse event

1 INTRODUCTION

Gliomas account for 80% of primary malignancies of the central nervous system (CNS). Glioblastomas (World Health Organization (WHO) Grade IV astrocytic tumors) account for 60–70% of gliomas and remain the most aggressive subtype. Glioblastoma occurs mostly in adults (median age of 64 years at diagnosis) with an estimated incidence of 2–3 cases per 100,000 people in Europe and North America. With 1- and 5-year overall survival (OS) rates of 29% and 3%, respectively, the prognosis of glioblastoma remains poor [Central Brain Tumor Registry of the United States 2011] and there is a need to develop more effective therapeutic approaches.

Tesevatinib (formerly known as KD019) is an orally-administered tyrosine kinase inhibitor that has been documented to inhibit multiple molecular drivers of tumor growth, including epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), Src, and vascular endothelial growth factor receptor 2 (VEGFR2).

This Statistical Analysis Plan (SAP) describes detailed statistical procedures to be used for study KD019-208 as specified in the protocol (Amendment No. 4, 03-Apr-2019): A Phase 2, Multicenter Study of tesevatinib Monotherapy in Patients with Recurrent Glioblastoma.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled “Guidance for Industry: Statistical Principles for Clinical Trials” and the most recent ICH-E3 Guideline, entitled “Guidance for Industry: Structure and Content of Clinical Study Reports.”

2 STUDY SUMMARY

2.1 Study Objectives

2.1.1 Primary Objectives

- To evaluate the efficacy of tesevatinib as measured by investigator-assessed progression-free survival rate at 6 months (PFS-6) in mITT population.

2.1.2 Primary Safety Objective

- To evaluate the safety and tolerability of tesevatinib in all treated subjects.

2.1.3 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of tesevatinib as measured by investigator-assessed progression-free survival rate at 6 months (PFS-6) in Subpopulations A and B.
- To evaluate the efficacy of tesevatinib as measured by the OS-9 rate, in all patients and in those in Subpopulations A and B
- To evaluate the efficacy of tesevatinib as measured by the PFS, in all patients and in those in Subpopulations A and B
- To evaluate the efficacy of tesevatinib as measured by the OS, in all patients and in those in Subpopulations A and B
- To evaluate the efficacy of tesevatinib as measured by ORR and DOR per RANO criteria, and DOR in all patients and in Subpopulations A and B
- To evaluate the efficacy of tesevatinib as measured by PFS-6, OS-9, ORR and DOR in:
  - $EGFRvIII^{pos}$ vs $EGFRvIII^{neg}$
  - $EGFR\ amplification^{pos}$ vs $EGFR\ amplification^{neg}$

2.2 Study Design

This is an open-label, single dose arm, multicenter, Phase 2 study to assess the activity of tesevatinib in patients (n =40) with recurrent glioblastoma. This study will be conducted at up to 10 sites in the United States.

Subjects meeting inclusion/exclusion criteria receive tesevatinib at the dose of 300 mg once daily. One cycle will be defined as 28 days of treatment. Subjects will be treated with study drug until disease progression or unacceptable toxicity occurs.

All patients also will be followed for a period of 30 days following their last dose of tesevatinib or until the patient starts a new treatment.

2.3 Visit Schedule and Study Assessment

The flow chart of visit schedule and study assessments is given in Table 1 of the KD019-208 Protocol.

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical programming and data analyses will be performed using SAS® Version 9.4 on Windows platform.

3.1.2 Changes from protocol

Changes from protocol in statistical methods are made in both primary and secondary analyses wherever necessary.

3.1.3 Sample Size Justification and power calculations:

The power calculation is based on simulations in the Weibull distribution to describe the progression and survival times. The estimation of PFS-6 is done using the Cox model. Based on a one-stage design, with a sample size of 40 patients in the overall population, a PFS-6 of 25% and median PFS of 4.5 months, the trial has 95% power to demonstrate an estimated PFS-6 >15%. Based on a one-sided test on a 5% significance level, the trial has 95% power to show a significant difference above the null hypothesis of 7% and 80% power to show a significant difference above 10%. The study is not powered to detect differences in the secondary endpoints.

3.1.4 General Considerations

General considerations for descriptive statistics and presentation for continuous and categorical data are given below.

3.1.4.1 Continuous variables

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation, median, minimum, and maximum.

Means, medians, standard deviations, and confidence intervals (CIs) will be reported to one decimal place more than the data reported on the case report form (CRF) or by the vendor. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the vendor. P-values will be reported to 4 decimal places.

3.1.4.2 Binary Endpoint and Other Categorical Variables

For endpoints with two possible outcomes such as alive/otherwise or response/otherwise within specific periods, the 95% confidence interval will be calculated with Clopper-Pearson method for survival rates or response rates. For

other categorical variables, the counts and percent of each category within a parameter will be calculated for observed data only. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the cohort or in the specified analysis population.

3.1.4.3 Progression-Free Survival (PFS) Endpoints

PFS is defined as the time from date of first dose to the date of disease progression or death, whichever happens first. For subjects who do not have an event (i.e. those who have not progressed, and are alive at the date of data cut-off or lost to follow-up), progression-free survival will be censored on that date.

PFS will be summarized using Kaplan-Meier methods for 25th percentile, median, and 75th percentile. 95% Confidence intervals will be calculated using Greenwood Formulation. Kaplan-Meier curves will be plotted for populations in the analysis.

3.1.4.4 Overall Survival (OS) Endpoints

OS is defined as the time from first dose until death due to any cause. In absence of confirmation of death, subjects will be censored either at the date that the subject was last known to be alive or the date of study cut-off, whichever comes earlier.

OS will be summarized using Kaplan-Meier methods for 25th percentile, median, and 75th percentile. 95% Confidence intervals will be calculated using Greenwood Formulation. Kaplan-Meier curves will be plotted for populations in the analysis.

3.1.5 Study Day

The Study Day for all assessments prior to the first study drug administration is calculated as the difference between the date of the event or measurement (e.g., adverse event [AE] onset date, assessment date, sample collection date) and the start date of study treatment. The day before the start of study treatment is Study Day -1.

The Study Day for all post-assessments after the first study drug administration is calculated as the difference between the date of the event or measurement (e.g., AE onset date, assessment date, sample collection date) and the start date of study treatment plus one day. The first day of study treatment is Study Day 1 with subsequent study days numbered sequentially thereafter.

3.1.6 Baseline

Baseline value is defined as the valid and last non-missing value obtained within 28 days prior to subject receiving the first study medication, unless otherwise stated under the related assessment section. Baseline can be the day before the first study medication or on the same day as the first study medication if a pre-dose assessment is available. Subjects without data on a parameter before the first study medication will have a missing baseline for this parameter.

3.1.7 Handling of Incomplete or Missing Data

Missing data will not be imputed in general and will be reported as missing in all listings. For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified.

Missing start and end dates for AE and concomitant medication (CM)

The assumption will be the worst or most conservative judgment when imputing AE and CM start and end dates. The purpose of imputing a start date is to help define whether the AE/CM started while taking study drug.

For a partial or missing start date:

- If the day is missing, the first day of the month will be imputed. If the missing day is the same as the month of first dose of study drug, then the first dose date will be imputed.
- If the day and month are missing, the first day of January will be imputed. If the year is the same as the first dose date, then the first dose date will be imputed.
- If the day is completely missing, the first dose date will be imputed. If the end date suggests it could have started prior to this, the first day of January of the same year as the end date will be imputed.
- When imputing a start date, the start date will ensure that the new imputed date is sensible, i.e., is prior to the end date of the AE or CM.

For a partial or missing end date:

- If the day is missing, the last day of the month or the last assessment date, whichever is earlier, will be imputed.
- If the day and month are missing, the 31st of December or the last assessment date, whichever is earlier, will be imputed
- If the date is completely missing, there will be a need to look at whether the AE/CM is still ongoing before imputing a date. If the ongoing flag is missing, then it will be assumed that AE is still present, or CM is still being taken (i.e., do

not impute a date). If the AE/CM has stopped, then the last assessment date will be imputed.

These data imputations are for categorization purpose only and will not be used in the listings.

If the assessment of the relationship of the AE to tesevatinib is missing, then it will be assumed that the AE is related to tesevatinib and the AE considered as such in the frequency tables of possibly related AEs. No imputation should be done at the data level.

Missing event dates

Event date will be imputed only when day is missing, and the purpose of imputing an event date is to most conservatively calculate time to event.

If the day is missing, the first (mid, last) day of the month will be imputed for undesired (neutral, desired) event. If the missing day is the same as the month of first dose of study drug, then the first dose date will be imputed for undesired event.

These data imputations are for time to event calculation only and will not be used in the listings.

3.2 Analysis Populations

The following populations will be analyzed:

Modified Intent-to-treat (mITT) Population: The primary population for efficacy analyses will be a Modified Intent-to-treat (mITT) Population defined as all subjects who receive at least 1 dose of study medication. The mITT Population will be used for tables of demography, baseline characteristics, and efficacy.

Safety Population: The Safety Population is defined as all subjects who receive at least 1 dose of study medication. In this study, the Safety Population is equivalent to the mITT Population.

Subpopulation: Two protocol defined subpopulations based on EGFR biomarkers EGFR at baseline are as follows

Subpopulation	Description
A	Patients with an assumed beneficial mutation (EGFR gene amplified glioblastoma)
B	Patients with an assumed beneficial mutation (EGFRvIII^{pos} glioblastoma)

These two biomarkers are the targets for tesevatinib treatment.

3.3 Subject Disposition and Evaluability

Subjects who failed screening (i.e., subjects who signed the informed consent were screened but never started the study treatment, and their basic demographics and any AE after signing the informed consent may have been collected in the CRF) will be excluded from any populations defined in Section 3.2. Therefore, these subjects will be excluded from any summary tables or listings.

The number of subjects discontinuing from the study and the primary reason for discontinuation will be summarized.

3.4 Protocol Deviations

All protocol deviations will be identified and classified as major or minor before clinical database lock and will be presented in a listing.

Major Deviation: Protocol deviation that may impact the accuracy, and/or reliability of the study data or that may impact subject rights, safety or well-being.

Minor Deviation: Protocol deviation that does not impact the accuracy, and/or reliability of the study data or subject rights, safety or well-being.

3.5 Demographics and Baseline Characteristics

3.5.1 Demographics

Subject demographics and baseline characteristics will be summarized for the mITT Population. Descriptive statistics will be provided for age, height, and weight.

3.5.2 Medical History

Medical history will be summarized by primary System Organ Class (SOC) and Preferred Term (PT). Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 (or higher) terminology.

3.5.3 Baseline GBM Disease Characteristics

- Months since first GBM diagnosis
- Months since recurrent GBM diagnosis
- Tumor Measurement
- Diagnosis of Prior Low Grade Astrocytoma

3.5.4 Other Baseline Characteristics

Other baseline values including Karnofsky Performance Scale (Appendix E; Karnofsky et al., 1949) and childbearing potential will also be summarized.

3.6 Prior and Concomitant Medications

3.6.1 Medications and procedures for GBM

- Prior radiotherapy
- Prior systemic therapy
- Corticosteroid use at baseline

3.6.2 Other Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary. Prior medications are defined as those medications that began and stopped before the start of study treatment. Concomitant medications are defined as medications taken after the start of study treatment and during the study period, including those began before but ongoing at the start of study treatment. If a medication start date is partially or fully missing and it is unclear as to whether the medication is prior or concomitant, it will be assumed that the medication is concomitant.

Number and percentage of incidence of prior and CM will be summarized according to Anatomical Therapeutic Class (ATC) and preferred drug name.

3.7 Treatment Compliance and Exposure

The amount of tesevatinib administered by visit and overall (total dose) will be tabulated and presented by patient in data listings. The distribution of the number of cycles achieved per patient will also be summarized. In addition, delays and all other alterations in tesevatinib administration will be presented

3.8 Primary Endpoint Analysis

3.8.1 Progression-Free Survival Rate at 6 Month (PFS-6)

Proportion of patients who are alive and not progressed at 6 months (24 weeks) will be analyzed with method as described in3.1.4.2. This analysis is based on mITT population. Patients whose survival or response status at 6 months (24 weeks) are unknown are not considered alive or progression free. Response Assessment in Neuro-Oncology (RANO) criteria are used to determine specific criteria for treatment response (Appendix 2 of the protocol.) in all endpoint analysis in this study.

3.8.2 Secondary Endpoint Analyses

3.8.2.1 PFS-6 in Subpopulations A and B, as well as combination of And B

Progression-Free Survival rate at 6 months will be analyzed with method as described in 3.1.3.2 respectively in subpopulations A and B, and the combination of A and B.

3.8.2.2 OS-9 in Subpopulations A and B, as well as in mITT

Survival rate at 9 months will be analyzed with method as described in 3.1.4.2 respectively in subpopulations A and B, and in mITT population.

3.8.2.3 PFS in Subpopulations A and B, as well as in mITT

PFS will be analyzed with method as described in 3.1.4.3 respectively in subpopulations A and B, and in mITT population.

3.8.2.4 OS in Subpopulations A and B, as well as in mITT

OS will be analyzed with method as described in 3.1.4.4 respectively in subpopulations A and B, and in mITT population.

3.8.2.5 Objective Response Rate (ORR) and DOR per RANO

ORR including CR or PR per RANO criteria will be analyzed with method as described in 3.1.4.2 respectively in subpopulations A and B, and in mITT population. This analysis will be performed in subpopulations A and B, and in mITT population.

For responders in above analyses, corresponding Duration of response is calculated as the time from first documented evidence of CR or PR (whichever status is recorded

first) until the first documented sign of disease progression or death due to any cause (whichever is the first). DOR will be summarized

It is defined for subjects with a confirmed CR or a confirmed PR. For subjects in the subset of responders who do not progress or die, duration of response will be analyzed with method as described in 3.1.4.3.

3.8.2.6 PFS-6, OS-9, ORR and DOR comparisons in the following subgroups

- EGFRvIII^{pos} vs EGFRvIII^{neg}
- EGFR amplification^{pos} vs EGFR amplification^{neg}

3.9 Patient-Reported Outcomes (PRO)

Patient-reported outcomes in M.D. Anderson Symptom Inventory – Brain Tumor questionnaire (MDASI-BT) will be listed for teach subject.

3.10 Safety Analysis

Safety assessments will include AEs, serious adverse events (SAEs), vital sign measurements, clinical laboratory evaluations (hematology and chemistry), and electrocardiograms (ECGs). Unscheduled visits for safety assessments will not be presented in summary tables but will be in listings. All safety analyses will be performed using the safety population.

3.10.1 Adverse Events

AEs will be coded using the MedDRA dictionary (Version 20.1 or higher). Treatment-emergent AEs (TEAEs) are any AE occurring or worsening in severity after the first administration of study medication. All AEs (including SAEs) will be graded using the 5-point Common Terminology Criteria for Adverse Events (CTCAE) V4.03 scale (mild, moderate, severe, life-threatening, or death). Causality with tesevatinib will be classified as: definitely related; probably related; possibly related; unlikely related; or not related.

The investigator will further assess the relationship of AEs to tesevatinib or the underlying disease.

The number and percentage of patients who experienced at least one TEAE as well as the number and percentage of patients who experienced AEs of each specific SOC and PT will be presented. For the presentation of AE incidences, the SOCs and the PTs within each SOC will be presented by decreasing total frequency. Tabulation by

maximum severity and relationship to tesevatinib will also be included by treatment group.

The TEAEs, Grade ≥ 3 TEAEs, SAEs, and TEAEs leading to dose modification/discontinuation will be summarized by treatment arm, SOC, and PT. These analyses will be repeated for events considered related (definitely related/probably related/possibly related) to tesevatinib.

Subject listings will be provided for SAEs, AEs resulting in study drug discontinuation and deaths.

Adverse events will also be presented in listings. Time to onset and duration of AEs will be included in listings, along with action taken and outcome.

3.10.2 Clinical Laboratory Evaluation

The summary statistics (including number, mean, standard deviation, median, minimum and maximum) of all laboratory variables and changes from baseline will be calculated for each visit or study assessment by treatment group. For parameters of white blood cell counts, neutrophils (absolute count), lymphocytes (absolute count), monocytes (absolute count), hemoglobin, platelets, ALP, ALT, aspartate aminotransaminase, gamma glutamyl transferase, total bilirubin, glomerular filtration rate, plots of mean/mean changes from baseline with the corresponding standard error will be displayed.

For shift tables, laboratory results will be classified using the CTCAE Version 4.03. All graded laboratory parameters will be summarized separately for hematology and biochemistry. Corresponding shift tables comparing baseline to the worst post-baseline grade within the treatment period will be provided.

3.10.3 Vital Signs

Descriptive statistics for vital signs (weight, temperature, blood pressure, pulse rate, and respiratory rate) values and the change from baseline will be presented for each scheduled assessment time point.

3.10.4 ECG

Descriptive statistics for ECG parameters (i.e., PR interval, QRS interval, and QTcF interval) at each time point with triplicate ECGs will be presented for the values and

change from baseline scores. (QTcF is the QT interval using Fridericia's correction which is calculated by $QTcF = QT/RR^{1/3}$.)

The number and percentage of subjects with observed QTcF values that satisfy the following conditions will be presented by treatment group and study visit and categorized as: ≤ 450 ms; > 450 to 480 ms; > 480 to 500 ms; and > 500 ms.

The number and percentage of subjects having change from baseline QTcF values that satisfy the following conditions will be presented by treatment group and study visit and categorized as: ≤ 0 ms; > 0 to ≤ 30 ms; > 30 to ≤ 60 ms; and > 60 ms.

3.11 Pharmacokinetic and Pharmacodynamic Analysis

PK serum concentration and all biomarkers will be summarized at each collection time-point.

4 LIST OF TABLES, FIGURES, AND LISTINGS

List of tables, figures, and listings will be completed in a separate document.