Official Title: A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Glioblastoma or Other Primary Central Nervous System Tumors Harboring Activating FGFR1-3 Alterations (FIGHT-209)

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Statistical Analysis Plan

INCB 54828-209

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Glioblastoma or Other Primary Central Nervous System Tumors Harboring Activating FGFR1-3 Alterations (FIGHT-209)

Product:	**Pemigatinib (INCB054828)**
IND Number:	**IND 158,135**
EudraCT Number:	**2021-004740-24**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803** **United States**
Protocol Version:	**Protocol Amendment 2 dated 19 JAN 2023**
CRF Approval Date:	**13 JUN 2023**
SAP Version:	**Original**
SAP Author:	[redacted] [redacted]**, Biostatistics**
Date of Plan:	**19 SEP 2023**

This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
BOR	best overall response
CE	European conformity (conformite europeenne)
CI	confidence interval
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire – Core 30
EQ-5D	EuroQoL Questionnaire 5D
FAS	full analysis set
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FGFR1-3	fibroblast growth factor receptors 1, 2, or 3
FGFR1/3	fibroblast growth factor receptors 1 and/or 3
GBM	glioblastoma
ICR	Independent Central Review
IDH	isocitrate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NANO	Neurologic Assessment in Neuro-Oncology
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PP	per protocol
PR	partial response
PT	preferred term

Abbreviation	Term
QoL	quality-of-life
QTc	QT interval corrected
RANO	Response Assessment in Neuro-Oncology
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TERT	telomerase reverse transcriptase
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 2, open-label, single-arm, multicenter study of pemigatinib in participants with recurrent GBM or other gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors that have recurred with an activating FGFR1-3 mutation or fusion/rearrangement. Section 2 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with pemigatinib.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCB 54828-209 Protocol Amendment 2.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 54828-209 Protocol Amendment 2 dated 19 JAN 2023 and CRFs approved on 13 JUN 2023. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of pemigatinib in participants with recurrent GBM with an activating FGFR1-3 mutation or fusion/rearrangement.	• ORR in Cohort A, defined as the proportion of participants in Cohort A who achieve a BOR of CR or PR based on RANO as determined by an ICR.
Secondary	
To determine the efficacy of pemigatinib in participants with recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors with an activating FGFR1-3 mutation or fusion/rearrangement.	• ORR in Cohort B, defined as the proportion of participants in Cohort B who achieve a BOR of CR or PR based on RANO as determined by an ICR. • ORR in Cohorts A and B combined, defined as the proportion of participants in Cohorts A and B who achieve a BOR of CR or PR based on RANO as determined by an ICR. • DOR in Cohorts A and B, respectively, defined as the time from first assessment of CR or PR until progressive disease (according to RANO and assessed by an ICR) or death (whichever occurs first). • ORR in each cohort as determined by investigator assessment. • DCR in Cohorts A and B, respectively, described as the proportion of participants who achieve a CR, PR, or SD as assessed by ICR. • PFS in Cohorts A and B, respectively, defined as the time from first dose until progressive disease (according to RANO and assessed by an ICR) or death (whichever occurs first). • OS in Cohorts A and B, respectively, defined as the time from first dose of study drug to death due to any cause.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
To determine the safety and tolerability of pemigatinib in participants with recurrent GBM or other recurrent gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors with an activating FGFR1-3 mutation or fusion/rearrangement.	• Safety and tolerability in each cohort, assessed by monitoring the frequency and severity of AEs by performing physical examinations, evaluating changes in vital signs and ECGs, and evaluating clinical laboratory blood samples according to NCI CTCAE v5.0. • Impact on-study treatment, assessed by monitoring the frequency of treatment interruptions, dose reductions, and withdrawal of study treatment due to AEs.
Exploratory	
[redacted]	

3. STUDY DESIGN

This is an open-label, monotherapy study of pemigatinib in participants with recurrent GBM or other gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors that have recurred with an activating FGFR1-3 mutation or fusion/rearrangement. The study design schema is presented in Figure 1. This study consists of 2 cohorts, Cohorts A and B, and will enroll approximately 82 participants in Cohort A and up to 82 participants in Cohort B. Participants will receive pemigatinib 13.5 mg once daily on a 2-week on-therapy and 1-week off-therapy schedule, as long as they are receiving benefit and have not met any criteria for study withdrawal. Participants with local laboratory test results (tissue is preferred but plasma-based molecular assays may be accepted after discussion with the medical monitor) documenting an activating FGFR1, FGFR2, or FGFR3 mutation or gene fusion/rearrangement are eligible to enroll, as long as the results meet the cohort criteria (refer to Protocol dated 19 JAN 2023 Appendix B) for eligible alterations). Participants will be required to have a documented FGFR1-3 rearrangement or actionable mutation from tumor tissue or plasma as determined by a locally qualified laboratory employing a molecular assay having a relevant mark of conformity for analytical performance (eg, Clinical Laboratory Improvement Amendments [US] or UK Conformity Assessed, CE, CE United Kingdom Northern Ireland, or others [outside of the US]) or a commercial report from the central laboratory to be eligible. Testing for IDH mutation status and O(6)-methylguanine-DNA methyltransferase promoter methylation status is required for all participants if not available prior to screening. For participants with astrocytic gliomas, testing for EGFR amplifications and/or whole chromosome 7 gain and whole chromosome 10 loss and/or TERT promoter mutations will be performed to establish the diagnosis of GBM. Testing for chromosome 1p/19q codeletion will be performed for all participants with oligodendrogliomas if not available prior to screening. Confirmatory testing through the sponsor-designated central genomics laboratory will be performed for all participants to confirm the presence of an eligible FGFR alteration; however, results the central genomics laboratory are not required before enrollment. Participants who have a commercial report at screening from the sponsor-designated central laboratory will not need to have a sample sent for confirmatory testing. Participants will be assigned to a cohort as follows:

- Cohort A: Participants with histopathologically proven, WHO Grade 4, IDH−wild-type GBM OR molecular diagnosis of IDH-wild-type, diffuse astrocytic glioma with molecular features of Grade 4 GBM per WHO (2021; astrocytic glioma requires presence of either amplification of EGFR, whole chromosome 7 gain and whole chromosome 10 loss, or TERT promoter mutation; Louis et al 2021) that is recurrent, harboring FGFR1-3 fusions or other rearrangements (FGFR1-3 in-frame fusions, any FGFR2 rearrangement, or FGFR1/3 rearrangement with known partner) or with a defined FGFR1-3 activating mutation or in-frame deletion. Only participants with FGFR fusions or rearrangements with an intact kinase domain (refer to Protocol dated 19 JAN 2023 Appendix B) are eligible (n = 82).

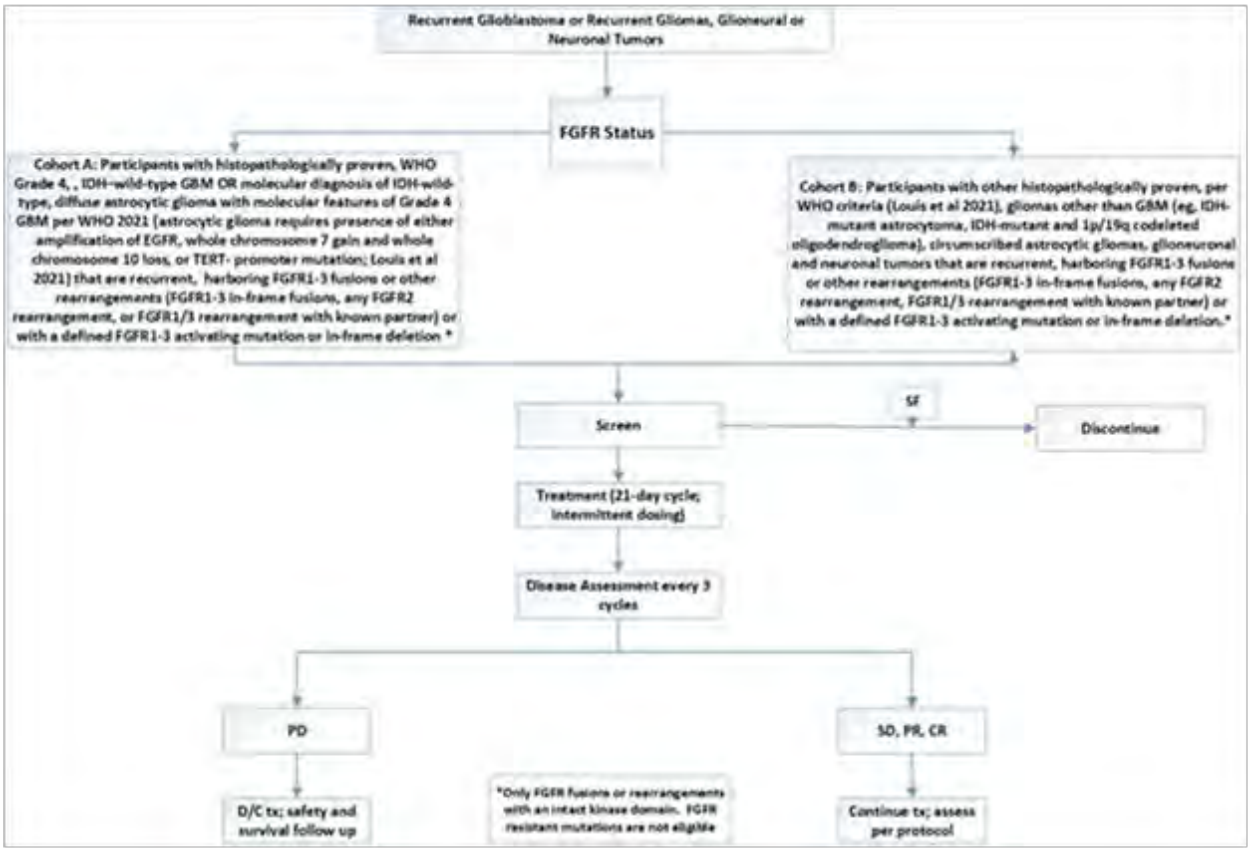
- Cohort B: Participants with other histopathologically proven, per WHO criteria (Louis et al 2021), gliomas other than GBM (eg, IDH-mutant astrocytoma, IDH-mutant and 1p/19q codeleted oligodendroglioma), circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors that are recurrent, harboring FGFR1-3 fusions or other rearrangements (FGFR1-3 in-frame fusions, any FGFR2 rearrangement, or FGFR1/3 rearrangement with known partner) or with a defined FGFR1-3 activating mutation or in-frame deletion. Only FGFR fusions or rearrangements with an intact kinase domain (refer to Protocol dated 19 JAN 2023 Appendix B) are eligible (n = up to 82).

Participants with known FGFR resistance mutations are not eligible.

There is no difference in the treatment regimen between the cohorts.

Treatment will start on Day 1. Participants will undergo regular safety and efficacy assessments during treatment. Participants can continue study drug administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported. For participants exhibiting disease progression based on local radiologic review, treatment will not be discontinued until confirmation by the ICR or unless the principal investigator believes it is in the best interest of the participant to discontinue treatment before receiving confirmation. A futility analysis is planned for Cohort A when approximately 25 participants are evaluable in this cohort. Cohort A can be closed if the prespecified minimal number of responders is not achieved for that cohort.

Figure 1: Study Design Schema



[a] Only FGFR fusions or rearrangements with an intact kinase domain. FGFR resistance mutations are not eligible.

3.1. Randomization

Not applicable.

3.2. Control of Type I Error

All statistical analyses are exploratory in nature. Unless otherwise specified, all CIs provided will be at the 95% confidence level.

3.3. Sample Size Considerations

The patient population selected for this trial includes participants with recurrent GBM or other gliomas, circumscribed astrocytic gliomas, and glioneuronal and neuronal tumors with an activating FGFR1-3 mutation or fusion/rearrangement. For these participants, there is no defined standard of care. Second surgery or reirradiation are options for selected participants. Alkylating chemotherapy, such as nitrosoureas or temozolomide rechallenge, as well as the vascular endothelial growth factor antibody bevacizumab, are alternative options. Response rates reported in randomized trials with chemotherapy in recurrent GBM have been less than 20% (Seystahl et al 2016). Approximately 82 participants are planned for the final analysis of the primary endpoint of ORR in Cohort A. With the assumed rate of 28% for pemigatinib, a sample size of approximately 82 participants would provide about 80% probability to have a 95% CI

with lower limit of > 15%. Up to 82 participants will be enrolled in Cohort B, which will provide an approximately 80% chance of observing at least 20 responders in this cohort if the underlying ORR is 28%.

3.4. Schedule of Assessments

Refer to Protocol Amendment 2 dated 19 JAN 2023 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of pemigatinib (INCB054828) is administered to the participants.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of pemigatinib.

When scheduled assessments and unscheduled assessments occur on the same day and the time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Dates

In general, values for missing dates will not be handled unless methods for handling missing dates are specified in this section or relevant sections. The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

When calculating the time since initial diagnosis of cancer or the time since reoccurrence of cancer, a partial cancer diagnosis or reoccurrence date will be handled as follows in the calculation:

- If only the day is missing, then the first day of the month will be used.
- If both the month and day are missing, then 01 JAN of the year will be used.
- If the diagnosis or reoccurrence date is completely missing, then the time since diagnosis or time since reoccurrence will not be calculated.

When the date of the last dose is used in deriving variables, such as duration of treatment or TEAE flag, a missing or partial date of the last dose will be handled as follows:

- If only the day is missing, then the earlier date of the last day of the month or the date that the participant discontinued treatment will be used.
- If both the month and day are missing, then the earlier date of 31 DEC of the year or the date that the participant discontinued treatment will be used.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, a partial date of the death date will be handled as follows in the calculation:

- If mmyyyy for the last known alive date = mmyyyy for the death date, then the death date will be set to the day after the last known alive date.
- If mmyyyy for the last known alive date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of pemigatinib is administered. The scheduled cycle length is 21 days. The actual Day 1 of subsequent cycles will correspond with the first day of administration of pemigatinib in that cycle. The date of the Day 1 of subsequent cycles recorded on the eCRF will be used as the Day 1 of the subsequent cycles.

4.1.6. Analysis Window

For parameters that will be summarized by visit, the nominal visit, as recorded on the eCRF, will be used. There will be no additional analysis windowing done based on the assessment date.

4.2. Variable Definitions

4.2.1. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of pemigatinib.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of pemigatinib and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of pemigatinib and is ongoing or ends during the course of study.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of pemigatinib. In the listing, it will be indicated whether a medication is only prior, only concomitant, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analyses are planned for this study as defined in Section 9.

5.2. Treatment Groups

This is an open-label, single treatment group study. Participants will be summarized by treatment cohort and by total. Cohort determination will be based on cancer types and FGFR mutation or gene rearrangement results. In the case that central testing of FGFR alterations do not pass test QC criteria, or is not feasible due to insufficient tissue, local laboratory results will be assessed to define the cohort assignments. Participants with central testing of FGFR alteration completed with passing test and FGFR alteration is unconfirmed will be assigned to Cohort Other.

5.3. Analysis Populations

5.3.1. Full Analysis Set

The FAS will include all enrolled participants who received at least 1 dose of pemigatinib in either Cohort A or Cohort B. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.

5.3.2. Per-Protocol Population

Participants in the FAS who are considered to be sufficiently compliant with the Protocol will compose the PP population.

Clinical review will be performed to identify those participants who are to be excluded from the PP population:

- Protocol deviation
- Concomitant medications as defined in Section 6.6 of the Protocol
- Dose administration and drug accountability listing

The determination of participants being considered for exclusion from the PP population by the clinical team will be prepared and signed before database lock.

The PP population will also be used for supportive sensitivity analyses for efficacy endpoints.

5.3.3. RANO-Evaluable Population

The RANO-evaluable population will include all participants in the FAS who completed a baseline scan and have at least 1 of the following criteria:

- ≥ 2 postbaseline objective tumor response assessments per ICR
- Withdrew from the study
- Discontinued treatment without post-treatment follow-up tumor assessment

The RANO-evaluable population will be used for ORR analysis at the interim analysis.

5.3.4. Safety Population

The safety population will include all enrolled participants who received at least 1 dose of pemigatinib. All safety analyses will be conducted using the safety population.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

6.1. Demographics, Baseline Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized for the FAS: age, sex, race, ethnicity, weight, and height.

6.1.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for the FAS: Karnofsky performance score, baseline phosphate, and baseline parathyroid hormone.

6.1.3. Disease History

Cancer type, the time since initial diagnosis, initial and current tumor grade (2021 WHO classification), initial and current infratentorial involvement, initial and current supratentorial involvement, initial and current cerebrospinal fluid involvement, initial and current cerebral hemisphere, histology at initial diagnosis, time since reoccurrence, current multifocal disease, and current sites of disease will be summarized for all participants in the FAS.

Time since diagnosis will be calculated as follows:

Time since diagnosis (years) = (Day 1 date – date of diagnosis + 1) / 365.25

Time since reoccurrence will be calculated as follows:

Time since reoccurrence (years) = (Day 1 date – date of reoccurrence + 1) / 365.25

6.1.4. Prior Therapy

The number of prior systemic cancer therapy regimens will be summarized for all participants in the FAS. The component drugs of prior systemic therapy regimens will be coded using the WHO Drug Dictionary. The number and percentage of participants who received each drug will be summarized by WHO drug class and WHO drug preferred term. The regimen name, start and stop dates, line/setting of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

The number of participants who received prior radiotherapy will be summarized for the FAS. The radiotherapy therapy technique, body location, start and stop dates, total dose, best response, date of progression, and number of fractions received will be listed.

The number of participants who had prior surgery or surgical procedure for the malignancies under study will be summarized for the FAS. The date and description of the surgery/procedure and extent of resection will be listed.

6.1.5. Medical History

For participants in the FAS, medical history will be summarized by assigned cohort. This summation will include the number and percentage of participants with a medical history event for each body system/organ class as documented on the eCRF.

6.2. Disposition of Participant

The number and percentage of participants who were treated, who were ongoing with study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, and who withdrew from the study with a primary reason for withdrawal will be summarized for the FAS. The number of participants enrolled by country and/or site will also be summarized by assigned cohort.

6.3. Protocol Deviations

Protocol deviations, as well as their categorization, will be summarized and listed for participants in the FAS.

6.4. Exposure

For participants in the safety population, exposure to pemigatinib will be summarized descriptively as the following:

- **Number of treatment cycles:**
  Number of cycles with a nonzero dose of pemigatinib
- **Duration of treatment with pemigatinib (days):**
  Date of last dose of pemigatinib – date of first dose of pemigatinib + 1
- **Average daily dose of pemigatinib (mg/day):**
  Total actual pemigatinib dose taken (mg) / duration of treatment with pemigatinib (days)

  Total actual dose taken will be calculated based on the information entered on the Drug Accountability eCRF. If there are dispensed drugs that have not yet been returned, the actual dose taken, starting from the dispense date of the unreturned drugs, will be imputed by the dose taken as reported on the Dosing eCRF.
- **Pemigatinib dose modifications:**
  Number of participants who had pemigatinib dose reduction and interruption

6.5. Study Drug Compliance

For participants in the safety population, overall compliance (%) for pemigatinib will be calculated for all participants as follows:

Compliance (%) = 100 × [total dose actually taken] / [total prescribed dose]

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the Drug Accountability eCRF. If there are dispensed drugs that have not yet been returned, the actual dose taken, starting from the dispense date of the unreturned drugs, will be imputed by the dose taken as reported on the Dosing eCRF.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of participants in the FAS for each prior and concomitant medication will be summarized by WHO drug class and WHO drug preferred term.

7. EFFICACY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

7.1. Efficacy Hypotheses

Not applicable.

7.2. Analysis of the Primary Efficacy Parameters

7.2.1. Primary Efficacy Analysis

The primary endpoint of the study is ORR in Cohort A. Objective response rate is defined as the proportion of participants who achieve a BOR of CR or PR, based on RANO (Wen et al 2010), as assessed by an independent centralized radiological review committee. Confirmation of CR and PR is required and documented in the Independent Central Review Charter. This primary analysis of ORR will be based on the FAS. Participants who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR. The 95% CI for the ORR will be estimated using the Clopper-Pearson method.

7.2.1.1. Response Criteria

Overall disease status will be categorized using RANO (Wen et al 2010). Participants will have their overall response evaluated as CR, PR, SD, PD, or NE at each postbaseline radiological assessment. Assessments using RANO are based on changes in enhancing measurable lesions, enhancing nonmeasurable/nontarget lesions, nonenhancing on T2-weighted or fluid-attenuated inversion recovery imaging (T2/FLAIR)/nontarget lesions, new lesions, steroid use, and clinical status.

7.2.1.2. Objective Response Rates and Best Overall Response

A participant is considered an objective responder if they have a BOR of CR or PR at any postbaseline visit before first PD.

In general, under RANO, BOR is the best response recorded postbaseline, before and including the first PD, in the order of CR, PR, SD, PD, and NE. The BOR will be determined from response assessments before or on the same day as new anticancer therapy. If any alternative cancer therapy, including palliative surgery and radiotherapy, is taken while on-study, then any subsequent assessments will be excluded from the BOR determination.

In the case of SD, measurements must meet the SD criteria at least once after the date of first dose at a minimum interval of 42 days. Participants who fail to meet this criterion will have either BOR of PD, if the next available assessment indicates PD or BOR of NE, if there is no additional assessment available.

7.2.2. Subgroup Analyses for Primary Endpoint

Subgroup analysis of the primary endpoint will be performed based on appropriate intrinsic and extrinsic factors if needed.

7.2.3. Sensitivity Analyses for Primary Endpoint

The primary endpoint will be analyzed using the PP population as a sensitivity analysis to the FAS.

7.3. Analysis of the Secondary Efficacy Parameters

7.3.1. Disease Control Rate

Disease control rate is defined as the proportion of participants who achieve a BOR of CR, PR, or SD, based on RANO (Wen et al 2010) and as assessed by an ICR. Confirmation of CR and PR is required and documented in the Independent Central Review Charter. This analysis will be based on FAS for participants in each cohort. Participants who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of DCR. The 95% CI for DCR will be calculated using exact method for binomial distribution in each cohort.

7.3.2. Progression-Free Survival

Progression-free survival is defined as the time from the date of first dose of pemigatinib to the date of the first documented progressive disease or death due to any cause, whichever is first. Progressive disease will be evaluated according to RANO (Wen et al 2010) and assessed by an ICR. Partial death dates will be handled using the rules described in Section 4.1.4. Participants who are alive without progression before the analysis cutoff date will be censored. Censoring for PFS will follow the algorithm outlined in Table 2, which is based on the FDA guidance for industry (FDA 2015, FDA 2018).

Table 2: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Day 1
No valid postbaseline response assessments	Censored	Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment including palliative surgery and radiotherapy started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing)

This analysis will be based on FAS. Progression-free survival data will be analyzed by the Kaplan-Meier method in Cohorts A and B, respectively. The number of participants who progressed or died and the number of participants censored will be summarized. The Kaplan-Meier curves for PFS will be presented by cohort. The Kaplan-Meier estimate of median PFS will be presented with its 95% CI. The 95% CI will be calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

7.3.3. Duration of Response

For objective responders, the DOR is defined as the time from the date that a participant first achieves CR or PR, until the date of first documented progressive disease or death, whichever is first. Responses and progressive disease will be evaluated based on RANO (Wen et al 2010) and assessed by an ICR. Partial death dates will be handled using the rules described in Section 4.1.4. Participants who are alive without progression before the analysis cutoff date will be censored. Censoring of DOR will follow the same algorithm as the censoring of PFS (see Section 7.3.2).

This analysis will be based on FAS. The DOR data will be analyzed by the Kaplan-Meier method in Cohorts A and B, respectively. The total number of responders, the number of participants who progressed or died, and the number of participants censored will be summarized. The Kaplan-Meier curves for DOR will be presented by cohort. The Kaplan-Meier estimate of median DOR will be presented with its 95% CI. The 95% CI will be calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

7.3.4. Overall Survival

Overall survival is defined as the interval between the date of first administration of pemigatinib to the date of death (due to any cause). Date of death will be determined using the Death Report, the Survival Follow-Up, and the Participant Status eCRFs. Participants who are lost-to-follow-up or still alive at the time of analysis will be right-censored at the earlier of the date the participant was last known alive and the clinical data cutoff date for the analysis. The last known alive date is defined as the later of the last study visit date and the date the participant was last known alive from the Survival Follow-Up and Participant Status eCRFs. Partial death dates will be handled using the rules described in Section 4.1.4.

This analysis will be based on FAS. Overall survival will be analyzed by the Kaplan-Meier method in Cohorts A and B, respectively. The number of participants who died and the number of participants censored will be summarized. The Kaplan-Meier curves for OS will be presented by cohorts. Median survival will be estimated using the Kaplan-Meier method. The 95% CIs for median survival time will be calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

7.3.5. Other Objective Response Rates

The ORR in Cohort B is defined as the proportion of participants in Cohort B who achieve a BOR of CR or PR, based on RANO (Wen et al 2010) and assessed by an ICR. It will be estimated with its 95% CI using the Clopper-Pearson method.

The ORR in Cohorts A and B combined is defined as the proportion of participants in Cohorts A and B who achieve a BOR of CR or PR, it will be based on RANO (Wen et al 2010) and assessed by an ICR. It will be estimated with its 95% CI using the Clopper-Pearson method.

The ORR in Cohorts A and B will be based on RANO (Wen et al 2010) and assessed by the investigator. It will be estimated with its 95% CI using the Clopper-Pearson method

7.4. Other Efficacy Analyses

7.4.1. Largest Percentage Reduction in Sum of Products of Perpendicular Diameters

For each participant in the FAS with measurable enhancing lesions at baseline, measurable enhancing lesion size will be measured by the sum of the products of the perpendicular diameters of all measurable enhancing lesions. The best percent change from baseline, defined as the largest decrease in measurable enhancing lesion size for each participant, will be summarized descriptively, and a waterfall plot of the best percent change will be generated. Note that for participants who only have increases in measurable enhancing lesion sizes from baseline, the smallest increase will be considered as the best change from baseline.

Per RANO criteria, a lesion deemed "too small to measure" will be assigned a value of 5 mm, for an axis that falls below the "too small to measure" threshold of 5 mm. For example, if both axes of measurable enhancing lesions are considered "too small to measure," then the lesion will be assigned a default value of 5×5 mm^2 for purposes of analysis. If only 1 axis falls below the "too small to measure" threshold, then only that measurement will be assigned a value of 5 mm. Likewise, measurable enhancing lesions identified as "not present" at postbaseline assessments will be assigned 0×0 mm^2 for this analysis. In the event a measurable enhancing lesion is unaccounted for in a particular postbaseline timepoint (ie, assessment missing or NE), then the overall sum of products of perpendicular diameters for measurable enhancing lesions will not be evaluable for that postbaseline timepoint.

7.4.2. NANO Scale

The NANO scale is a disease-specific clinician-reported outcome assessment tool to measure neurological function across 9 relevant neurologic domains most relevant to participants with intracranial malignant tumors (ie, gait, strength, upper extremity ataxia, sensation, visual fields, facial strength, language, level of consciousness, and behavior; Nayak et al 2017). Relevant and discrete levels of function were defined for each neurological domain (see Appendix B).

The NANO scale provides an objective and quantifiable metric to score neurological function at each planned study visit. Moreover, it objectively defines clinical parameters of response and progression related to underlying tumor activity. When the NANO is combined with the radiological disease assessment, the result generates a robust measure of outcome for patients.

A total NANO score is generated at each scheduled assessment. The NANO scale for each domain at the scheduled assessment times will be summarized and listed. For the total NANO score, baseline value, postbaseline value, and change from baseline will be summarized descriptively by planned study visits.

7.5. Analysis of Exploratory Efficacy Variables

7.5.1. Karnofsky Performance Status Score

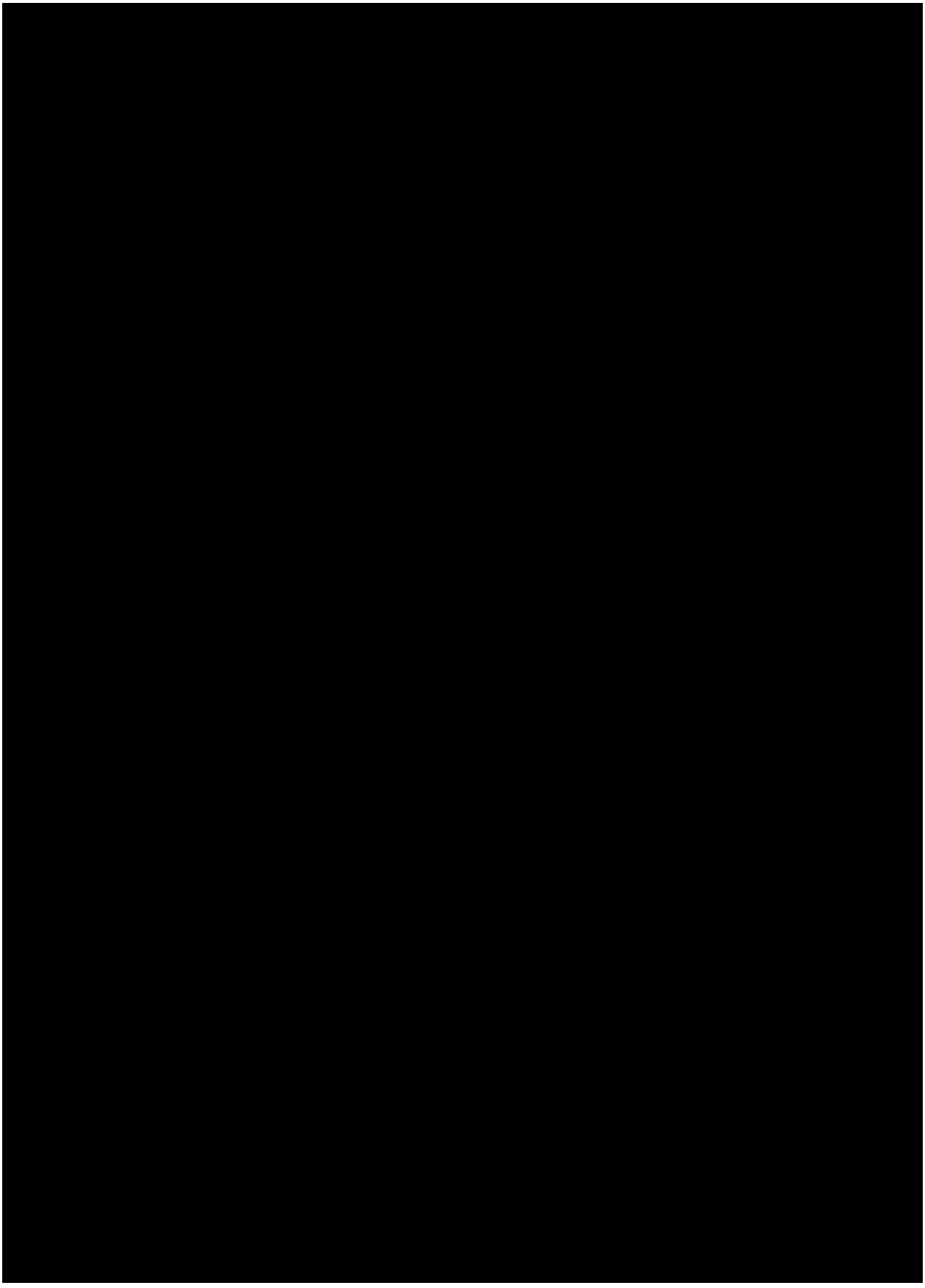
The Karnofsky Performance Status is a standard way of measuring the ability of participants with cancer to perform ordinary tasks. The scores range from 0 to 100 (see Table 3) and will be assessed at scheduled assessment times. It is recommended, when possible, that a participant's performance status is assessed by the same person throughout the study.

The Karnofsky Performance Status scores and changes in status at scheduled assessment times will be summarized. Shift tables will be presented showing change in Karnofsky Performance Status scores from baseline to worst postbaseline score.

Table 3: Karnofsky Performance Status Scores

Score	Performance Status
100	Normal, no complaints; no evidence of disease.
90	Able to carry on normal activity, minor signs or symptoms of disease.
80	Normal activity with effort, some symptoms or signs of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requiring occasional assistance, can take care of most personal requirements.
50	Requires considerable assistance, requires frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospital admission indicated but no risk of death.
20	Very ill, urgently requiring hospital admission, requires supportive measures or treatment.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

Source: Terret et al 2011.



8. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

8.1. General Considerations

The analyses in this section will be provided for the safety population. Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique preferred terms reported on relatively few participants.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug until 30 days after the last dose of study drug. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE v5.0. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v5.0 criteria, it will be graded on a scale of 1 to 5 as follows: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, and 5 = fatal. All toxicities will be graded based on the worst level reached, not the level they may have reached if they had not been treated. When the intensity of an AE changes over time for a reporting period (eg, between visits), each change in intensity will be reported as an AE until the event resolves.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

8.2.2. Clinically Notable Adverse Events

Specific groupings of clinically notable AEs will be considered and the number of participants with at least 1 event within each grouping will be reported. Such groups consist of AEs for which there is a specific clinical interest in connection with pemigatinib or AEs that are similar in nature (although not identical). The groups are defined in Table 5. All clinically notable AEs are defined through PTs, as per the current MedDRA v26.0.

Table 5: Clinically Notable Adverse Events by Grouping

Categories	Preferred Terms
Serous retinal detachment	Serous retinal detachment, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal detachment, subretinal fluid, chorioretinopathy, retinal pigment epitheliopathy, chorioretinal disorder, retinopathy, maculopathy, retinal disorder, retinal thickening, chorioretinal folds, chorioretinal scar
Nail toxicity	Nail toxicity, nail bed tenderness, nail bed disorder, nail bed bleeding, nail disorder, nail discolouration, nail discomfort, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, paronychia, fungal paronychia
Hyperphosphatemia	Hyperphosphataemia, blood phosphorus increased
Hypophosphatemia	Hypophosphataemia, blood phosphorus decreased
Dry eye	Dry eye, meibomian gland dysfunction, lacrimation increased, keratitis, punctate keratitis, pinguecula, pterygium
Eyelash changes	Eyelash changes, growth of eyelashes, trichiasis, trichomegaly
Vision blurred	Vision blurred, visual impairment, visual acuity reduced
Vitreous detachment	Vitreous detachment, vitreous floaters

8.2.3. Adverse Event Summaries

An overall summary of AEs by cohorts will include the following:

- Number (%) of participants who had any TEAEs
- Number (%) of participants who had any serious TEAEs
- Number (%) of participants who had any Grade 3 or higher TEAEs
- Number (%) of participants who had any TEAEs related to pemigatinib
- Number (%) of participants who temporarily interrupted pemigatinib because of TEAEs
- Number (%) of participants who permanently discontinued pemigatinib because of TEAEs
- Number (%) of participants who had pemigatinib dose reductions because of TEAEs
- Number (%) of participants who had any fatal TEAEs

The following summaries will be produced by MedDRA term:

- Summary of TEAEs by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT in decreasing order of frequency
- Summary of TEAEs by MedDRA SOC, PT, and maximum severity
- Summary of Grade 3 or higher TEAEs by MedDRA SOC and PT
- Summary of Grade 3 or higher TEAEs by MedDRA PT in decreasing order of frequency

- Summary of serious TEAEs by MedDRA SOC and PT
- Summary of serious TEAEs by MedDRA PT in decreasing order of frequency
- Summary of pemigatinib treatment-related TEAEs by MedDRA SOC and PT
- Summary of pemigatinib treatment-related TEAEs by MedDRA PT in decreasing order of frequency
- Summary of Grade 3 or higher pemigatinib treatment-related TEAEs by MedDRA SOC and PT
- Summary of pemigatinib treatment-related serious TEAEs by MedDRA SOC and PT
- Summary of TEAEs with a fatal outcome by MedDRA SOC and PT
- Summary of TEAEs leading to pemigatinib dose reduction by MedDRA SOC and PT
- Summary of TEAEs leading to pemigatinib dose interruption by MedDRA SOC and PT
- Summary of TEAEs leading to discontinuation of pemigatinib by MedDRA SOC and PT
- Summary of sponsor-defined clinically notable TEAEs by category and PT
- Summary of Grade 3 or higher sponsor-defined clinically notable TEAEs by category and PT
- Summary of serious sponsor-defined clinically notable TEAEs by category and PT
- Summary of sponsor-defined clinically notable TEAEs leading to pemigatinib dose reduction by category and PT
- Summary of sponsor-defined clinically notable TEAEs leading to pemigatinib dose interruption by category and PT
- Summary of sponsor-defined clinically notable TEAEs leading to discontinuation of pemigatinib by category and PT

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit for numeric laboratory parameters. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values will be assessed for severity based on the numerical component of CTCAE v5.0.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from central laboratories will be reported in SI units. All tests with numeric values will have a unique unit. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units.

Numeric laboratory values, baseline values, postbaseline values, change from baseline, and percentage change from baseline will be summarized descriptively by visit. The number and percentage of participants with the laboratory values being low, normal, and high will be summarized by visit. In addition, mean change from baseline will be plotted over time for selected laboratory parameters, including phosphate.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v5.0. Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category. The number of participants who experienced worsening of laboratory abnormalities will be summarized by maximum severity.

8.3.3. Potential Drug-Induced Liver Injuries

Participants with elevated alanine aminotransferase or aspartate aminotransferase $\geq 3 \times$ ULN range and alkaline phosphatase $< 2 \times$ ULN range accompanied by total bilirubin $\geq 2 \times$ ULN range at the same visit will be listed by cohort.

8.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, body temperature, respiratory rate, and weight will be summarized descriptively.

Normal ranges for vital sign values are defined in Table 6. For participants exhibiting vital sign abnormalities, the abnormal values will be listed along with their cohort. Alert vital signs are defined as an absolute value outside the defined normal range and percentage change greater than 25%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 6: Normal Ranges for Vital Sign Values

Parameter	High Threshold	Low Threshold
Systolic blood pressure	≤ 155 mmHg	≥ 85 mmHg
Diastolic blood pressure	≤ 100 mmHg	≥ 40 mmHg
Pulse	≤ 100 bpm	≥ 45 bpm
Temperature	≤ 38°C	≥ 35.5°C
Respiratory rate	≤ 24 breaths/min	≥ 8 breaths/min

8.5. Electrocardiograms

Twelve-lead ECGs, including the HR, PR, QT, QRS, and QTc intervals, will be obtained for each participant during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of pemigatinib.

Normal ranges for ECG values are defined in Table 7. The ECG values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Participants exhibiting ECG abnormalities will be listed with study visit and assigned cohort. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Outliers of QT and QTc values, defined as absolute values > 450 millisecond, > 500 millisecond, or change from baseline > 30 millisecond, will be summarized.

Table 7: Normal Ranges for Electrocardiogram Intervals

Parameter	High Threshold	Low Threshold
PR	≤ 220 ms	≥ 75 ms
HR	≤ 100 bpm	≥ 45 bpm
QT	≤ 500 ms	≥ 300 ms
QRS	≤ 120 ms	≥ 50 ms
QTc	≤ 460 ms	≥ 295 ms

9. INTERIM ANALYSES

As limited efficacy data are available for pemigatinib in GBM, a futility analysis will be performed for Cohort A when approximately 25 participants are enrolled into this cohort and have at least 2 postbaseline objective tumor response assessments per ICR or are withdrawn from the study or discontinued from treatment without post-treatment tumor assessments. Cohort A can be closed for futility if ≤ 4 responders are observed in the RANO-evaluable population, for which there is $< 5\%$ probability of claiming ORR $> 15\%$ at final analysis. Given the small sample size at the interim analysis and the possible confounding factors, this rule is for internal guidance and is nonbinding. The totality of data collected, including responders, as well as participants with SD, will be taken into account in the decision to continue or terminate Cohort A.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 8.

Table 8: Statistical Analysis Plan Versions

SAP Version	Date
Original	19 SEP 2023

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

11. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Food and Drug Administration (FDA). Guidance for industry: clinical trial endpoints for the approval of non–small cell lung cancer. Drugs and Biologics. 2015.

Food and Drug Administration (FDA). Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2018.

Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York: Springer-Verlag. 1997.

Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol 2021;23:1231-1251.

Nayak L, DeAngelis LM, Brandes AA, et al. The neurologic assessment in neuro-oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria. Neuro Oncol 2017;19:625-635.

Seystahl K, Wick W, Weller M. Therapeutic options in recurrent glioblastoma—an update. Crit Rev Oncol Hematol. 2016;99:389-408.

Terret C, Albrand G, Moncenix G, Droz JP. Karnofsky Performance Scale (KPS) or Physical Performance Test (PPT)? That is the question. Crit Rev Oncol Hematol 2011;77:142-147.

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol 2010;28:1963-1972.

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the Clinical Study Report. Shells are provided in a separate document for tables that are not in the Standard Safety Tables v1.13.

The lists of tables, figures, and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard
Baseline and Demographic Characteristics			
1.1.1	Analysis Populations	All enrolled	X
1.1.2	Summary of Participant Disposition	FAS	X
1.1.3	Summary of Number of Participants Enrolled by Country and Site	FAS	X
1.1.4	Summary of Protocol Deviations	FAS	X
1.2.1	Summary of Demographics and Baseline Characteristics	FAS	X
1.3.1	Summary of Baseline Disease Characteristics	FAS	X
1.3.3	Summary of Prior Systemic Cancer Therapy	FAS	X
1.4.1	Summary of Prior Medications	FAS	X
1.4.2	Summary of Concomitant Medications	FAS	X
1.5.1	Summary of General Medical History	FAS	X
Efficacy			
2.1.1	Summary of Best Overall Response and Objective Response Rate – Cohort A	FAS	
2.1.2	Summary of Best Overall Response and Objective Response Rate – Cohort A	PP	
2.2.1	Summary of Best Overall Response and Objective Response Rate – Cohort B	FAS	
2.2.2	Summary of Best Overall Response and Objective Response Rate – Cohort A and B Combined	FAS	
2.2.3	Summary of Disease Control Rate	FAS	
2.2.4	Summary of Progression-Free Survival	FAS	
2.2.5	Summary of Duration of Response	FAS	
2.2.6	Summary of Overall Survival	FAS	
2.2.7	Summary of Best Change in Measurable Enhancing Lesion Size	FAS	
[redacted]			
2.3.3	Summary of NANO Scale	FAS	
2.3.4.1	Summary of Karnofsky Performance Status Score	FAS	
2.3.4.2	Shift Summary of Karnofsky Performance Status Score – to the Worst Postbaseline Value	FAS	X
Safety			
3.1.1	Summary of Exposure and Duration of Exposure to Pemigatinib	Safety	X
3.1.2	Summary of Study Drug Compliance	Safety	X
3.1.3	Summary of Dose Modification	Safety	X
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X

Table No.	Title	Population	Standard
3.2.6	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.7	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.8	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.9	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.10	Summary of Pemigatinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.11	Summary of Pemigatinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.14	Summary of Grade 3 or Higher Pemigatinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.15	Summary of Pemigatinib Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.16	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.18	Summary of Treatment-Emergent Adverse Events Leading to Pemigatinib Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.19	Summary of Treatment-Emergent Adverse Events Leading to Pemigatinib Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.20	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Pemigatinib by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.21	Summary of Sponsor-Defined Clinically Notable TEAEs by Category and Preferred Term	Safety	X
3.2.22	Summary of Grade 3 or Higher Sponsor-Defined Clinically Notable TEAEs by Category and Preferred Term	Safety	X
3.2.23	Summary of Serious Sponsor-Defined Clinically Notable TEAEs by Category and Preferred Term	Safety	X
3.2.24	Summary of Sponsor-Defined Clinically Notable TEAEs Leading to Pemigatinib Dose Reduction by Category and Preferred Term	Safety	X
3.2.25	Summary of Sponsor-Defined Clinically Notable TEAEs Leading to Pemigatinib Dose Interruption by Category and Preferred Term	Safety	X
3.2.26	Summary of Sponsor-Defined Clinically Notable TEAEs Leading to Discontinuation of Pemigatinib by Category and Preferred Term	Safety	X
3.3.1.1	Summary of Laboratory Values – Hematology	Safety	X
3.3.1.2	Summary of Laboratory Values – Chemistry	Safety	X
3.3.1.3	Summary of Laboratory Values – Coagulation	Safety	X
3.3.1.4	Summary of Laboratory Values – Endocrine	Safety	X
3.3.3.1	Shift Summary of Hematology Laboratory Values in CTCAE Grade – to the Worst Abnormal Value	Safety	X
3.3.3.2	Shift Summary of Chemistry Laboratory Values in CTCAE Grade – to the Worst Abnormal Value	Safety	X
3.3.3.3	Shift Summary of Coagulation Laboratory Values in CTCAE Grade – to the Worst Abnormal Value	Safety	X
3.3.3.4	Treatment-Emergent Worsening of Laboratory Abnormalities – Hematology	Safety	X
3.3.3.5	Treatment-Emergent Worsening of Laboratory Abnormalities – Chemistry	Safety	X
3.3.3.6	Treatment-Emergent Worsening of Laboratory Abnormalities – Coagulation	Safety	X
3.4.1	Summary of Systolic Blood Pressure	Safety	X
3.4.2	Summary of Diastolic Blood Pressure	Safety	X
3.4.3	Summary of Pulse	Safety	X

Table No.	Title	Population	Standard
3.4.4	Summary of Respiratory Rate	Safety	X
3.4.5	Summary of Body Temperature	Safety	X
3.4.6	Summary of Weight	Safety	X
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	Safety	X
3.5.2	Summary of QRS Interval (ms) From 12-Lead ECG	Safety	X
3.5.3	Summary of QT Interval (ms) From 12-Lead ECG	Safety	X
3.5.4	Summary of QTc Interval (ms) From 12-Lead ECG	Safety	X
3.5.7	Summary of HR (bpm) From 12-Lead ECG	Safety	X
3.5.8	Summary of Outliers of QT and QTc Interval Values (ms) From 12-Lead ECG	Safety	X
3.5.9	Summary of Clinically Significant ECG Abnormality	Safety	X

Figures

Figure No.	Title
4.1.1	Kaplan-Meier Estimates of Progression -Free Survival
4.2.1	Kaplan-Meier Estimates of Duration of Response
4.2.2	Kaplan-Meier Estimates of Overall Survival
4.3.1	Waterfall Plot of Best Percentage Change in Measurable Enhancing Lesion Size
4.3.2	Swimmer Plot of Duration of Treatment
4.6.1	Line Graph of Selected Laboratory Values by Study Visit

Listings

Listing No.	Title
2.1.1	Participant Enrollment and Disposition Status
2.1.2	Participant Inclusion and Exclusion Criteria Violations
2.2.1	Protocol Deviations
2.3.1	Analysis Population
2.4.1	Demographic and Baseline Characteristics
2.4.2	Disease History
2.4.3	Prior Radiotherapy
2.4.4	Prior Systemic Therapy
2.4.5	Prior Surgery or Surgical Procedure
2.4.6	Medical History
2.4.7	Prior and Concomitant Medication
2.4.8	Current Radiotherapy
2.4.9	Procedures and Nondrug Therapy
2.4.10	Post Radiotherapy
2.4.11	Post Therapy
2.5.1	Study Drug Compliance
2.5.2	Study Drug Administration
2.6.1	Deaths
2.6.2	Best Overall Response, Duration of Response, Progression-Free Survival, and Overall Survival
2.6.3	Overall Response Assessment by Visit
2.6.4	Response Assessment: Measurable Disease
2.6.5	Response Assessment: Nonmeasurable Disease
2.6.6	Response Assessment: New Lesions
[redacted]	
2.6.8	FGFR Alterations

Listing No.	Title
2.6.9	NANO Scale
2.6.10	Karnofsky Performance Status Scores
[redacted]	
2.6.13	Corticosteroid Intake
2.7.1	Adverse Events
2.7.2	Serious Adverse Events
2.7.3	Grade 3 and Higher Adverse Events
2.7.4	Fatal Adverse Events
2.7.5	Treatment-Related Adverse Events
2.7.6	Adverse Events Leading to Interruption, Reduction, or Discontinuation of Pemigatinib
2.7.7	Sponsor-Defined Clinically Notable Adverse Events
2.8.1	Clinical Laboratory Values – Hematology
2.8.2	Clinical Laboratory Values – Chemistry
2.8.3	Clinical Laboratory Values – Coagulation
2.8.4	Clinical Laboratory Values – Endocrine
2.8.5	Abnormal Clinical Laboratory Values – Hematology
2.8.6	Abnormal Clinical Laboratory Values – Chemistry
2.8.7	Abnormal Clinical Laboratory Values – Coagulation
2.8.8	Potential Drug-Induced Liver Injuries
2.9.1	Vital Signs
2.9.2	Abnormal Vital Sign Values
2.9.3	Alert Vital Sign Values
2.10.1	12-Lead ECG Values
2.10.2	Abnormal 12-Lead ECG Values
2.10.3	Alert 12-Lead ECG Values
2.11.1	Eye Examinations

APPENDIX B. NANO SCALE

The following appendix contains the scoring assessment based on the clinical evaluation of observation and testing performance of participants in this study. Please refer to Section 7.4.2 for more details on scoring parameters.

Neurologic Assessment in Neuro-Oncology (NANO) Scale

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check one answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately because of preexisting conditions, comorbid events, or concurrent medications.

Patient identifier: _____

Date assessment performed (day/month/year): _____

Study time point (ie, baseline, cycle 1, day 1, etc): _____

Assessment performed by (please print name): _____

Domains	Key Considerations
Gait 0 ☐ Normal 1 ☐ Abnormal but walks without assistance 2 ☐ Abnormal and requires assistance (companion, cane, walker, etc.) 3 ☐ Unable to walk ☐ Not assessed ☐ Not evaluable	• Walking is ideally assessed by at least 10 steps
Strength 0 ☐ Normal 1 ☐ Movement present but decreased against resistance 2 ☐ Movement present but none against resistance 3 ☐ No movement ☐ Not assessed ☐ Not evaluable	• Test each limb separately • Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups • Score should reflect worst performing area • Patients with baseline level 3 function in one major muscle group/limb can be scored based on assessment of other major muscle groups/limb

Ataxia (Upper Extremity)

- 0 ☐ Able to finger-to-nose touch without difficulty
- 1 ☐ Able to finger-to-nose touch but difficult
- 2 ☐ Unable to finger-to-nose touch
- ☐ Not assessed
- ☐ Not evaluable

- Nonevaluable if strength is compromised
- Trunk/lower extremities assessed by gait domain
- Particularly important for patients with brainstem and cerebellar tumors
- Score based on best response of at least 3 attempts

Sensation

- 0 ☐ Normal
- 1 ☐ Decreased but aware of sensory modality
- 2 ☐ Unaware of sensory modality
- ☐ Not assessed
- ☐ Not evaluable

- Recommend evaluating major body areas separately (face, limbs, and trunk)
- Score should reflect worst performing area
- Sensory modality includes but not limited to light touch, pinprick, temperature, and proprioception
- Patients with baseline level 2 function in one major body area can be scored based on assessment of other major body areas

Visual Fields

- 0 ☐ Normal
- 1 ☐ Inconsistent or equivocal partial hemianopsia (≥quadrantanopsia)
- 2 ☐ Consistent or unequivocal partial hemianopsia (≥quadrantanopsia)
- 3 ☐ Complete hemianopsia
- ☐ Not assessed
- ☐ Not evaluable

- Patients who require corrective lenses should be evaluated while wearing corrective lenses
- Each eye should be evaluated, and score should reflect the worst performing eye

Facial Strength

- 0 ☐ Normal
- 1 ☐ Mild/moderate weakness
- 2 ☐ Severe facial weakness
- ☐ Not assessed
- ☐ Not evaluable

- Particularly important for brainstem tumors
- Weakness includes nasolabial fold flattening, asymmetric smile, and difficulty elevating eyebrows

Language

0 ☐ Normal
1 ☐ Abnormal but easily conveys meaning to examiner
2 ☐ Abnormal and difficulty conveying meaning to examiner
3 ☐ Abnormal; if verbal, unable to convey meaning to examiner; OR nonverbal (mute/global aphasia)
☐ Not assessed
☐ Not evaluable

- Assess based on spoken speech; nonverbal cues or writing should not be included
- **Level 1**: Includes word-finding difficulty; few paraphasic errors/neologisms/word substitutions; but able to form sentences (full/broken)
- **Level 2**: Includes inability to form sentences (<4 words per phrase/sentence); limited word output; fluent but "empty" speech

Level of Consciousness

0 ☐ Normal
1 ☐ Drowsy (easily arousable)
2 ☐ Somnolent (difficult to arouse)
3 ☐ Unarousable/coma
☐ Not assessed
☐ Not evaluable

- None

Behavior

0 ☐ Normal
1 ☐ Mild/moderate alteration
2 ☐ Severe alteration
☐ Not assessed
☐ Not evaluable

- Particularly important for frontal lobe tumors
- Alteration includes but is not limited to apathy, disinhibition, and confusion
- Consider subclinical seizures for significant alteration