NOVARTIS

Clinical Development

BGJ398

Trial Protocol CBGJ398X2201 / NCT01975701

A Phase 2, multicenter, open-label study of BGJ398 in patients with recurrent resectable or unresectable Glioblastoma

Statistical Analysis Plan (SAP)

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21-Dec-2017	1.0	BGJ398X2201 SAP amendment 1 after 2017 dry run

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List of abbreviations

AE	Adverse Event
ALT/SGPT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST/SOPT	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
CL	Clearance
████	████████████
██	████████
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CSP	Clinical Study Protocol
CSR	Clinical study report
CSR addendum	An addendum to CSR that captures all the additional information that is not included in the CSR
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage Administration Record

DDS	Dose-determining set
ECG	Electrocardiogram
(e)CRF	Electronic Case Report/Record Form
EGFR	Epidermal growth factor receptor
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FGF	Fibroblast growth factor
FGFR	Fibroblast Growth Factor receptor
GBM	Glioblastoma
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
IB	Investigators Brochure
IC_{50}	Half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LLN	Lower limit of Normal
LLOQ	Lower Limit of Quantification
LPLT	Last patient last treatment
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
N	Sample size
NA	Not applicable
OC	Oral contraception
ORR	Objective Response Rate
OS	Overall survival
p.o.	*per os*/by mouth/orally
██	████████████████
██	█████████
PFS	Progression-free survival
PFS6	Progression-free survival at 6 months
██	█████████
PPS	Per protocol set
PR	Partial Response
q.d.	once a day
QTcB	Q-T interval in the ECG (corrected according to the formula of Bazett)
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
RANO	Response Assessment in Neuro-Oncology

RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
SAE	Serious Adverse Event
SoC	Standard of Care Treatment
TACC	Transforming acidic coiled-coil
███	████████████████████████████
U.S. FDA	the U.S. Food and Drug Administration
US	United States
WBC	White Blood Cell

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CBGJ398X2201, a multi-center, open label, phase II study of BGJ398 for the treatment of patients with recurrent GBM and/or other glioma subtypes, whose tumors harbor FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, FGFR2, or FGFR3 gene.

The content of this SAP is based on protocol CBGJ398X2201 Amendment version 2. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data. Detailed tables, figures and listings can be found in TFL shells version 1.0.

1.1 Study design

The study is planned to enroll patients with recurrent GBM in two groups. Non Surgery Group enrolls patients who are not candidates for surgery. Patients in Non Surgery Group receive BGJ398 on a three weeks on, one week off schedule. Surgery Group enrolls patients who are surgical candidates. Patients in Surgery Group receive BGJ398 for 5-10 days prior to surgery. After recovery of surgery (a minimum of two weeks and no more than six weeks following surgery), patients in Surgery Group receive BGJ398 on a three weeks on, one week off schedule. Patients from both Non Surgery Group and Surgery Group are evaluated for tumor response and progression by Gd-enhanced MRI every 8 weeks until disease progression/discontinuation from study using RANO criteria.

The study plans to enroll 34 adult patients with histologically confirmed recurrent GBM and/or other glioma subtypes with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, 2, or 3.

Figure 1-1   Study design

1.2   Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1   Objectives and related endpoints

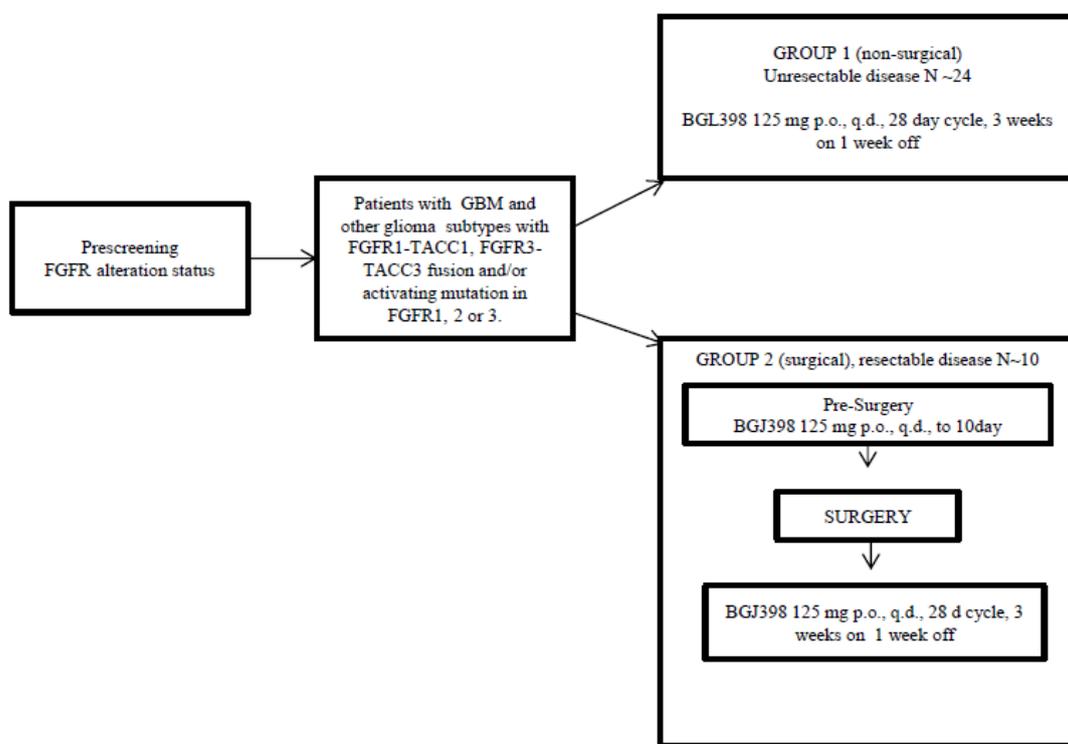| Objective	Endpoint
Primary	
To assess the anti-tumor activity of BGJ398 for patients with GBM and/or other glioma subtypes with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1,2 or 3, based on PFS6	PFS rate at 6 months as defined by RANO criteria as assessed by the investigator
Secondary	
To further assess the anti-tumor activity of BGJ398 for patients with GBM and/or other glioma subtypes with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1,2or 3, based on ORR	ORR (patients with measurable disease) as defined by RANO criteria as assessed by the investigator

Objective	Endpoint
To further assess the anti-tumor activity of BGJ398 for patients with GBM and/or other glioma subtypes with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation with in FGFR1,2or 3, based on OS	Overall survival (OS)
To characterize the safety and tolerability of BGJ398	Safety: type, frequency, and severity of AEs and SAEs; Tolerability: dose interruptions, reductions and dose intensity, and evaluations of laboratory values

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis personnel. SAS® version 9.4 will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The study data will be analyzed and reported (in a primary CSR if final DBL has not occurred) based on all patient's data when all patients have completed at least 6 cycles of treatment or discontinued the study. The primary CSR will include all outputs planned in the TFL Shells documents. Additional data of any patients continuing to receive BGJ398 beyond the cut-off date, as allowed by the CSP, will be summarized in a final CSR that will be prepared once all patients have discontinued the study or at the end of the study (end of survival follow up period) which is one year after the last patient's last dose of study treatment, whichever occurs first.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all participating centers will be combined for the analysis, so that an adequate number of patients will be available for analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables, a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug refers to the BGJ398 only.

Study treatment = investigational drug.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug BGJ398 is administered and recorded on the Dosage Administration Record (DAR) (e)CRF. The date of first administration of investigational drug will also be referred as the start date of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as is the last date when a nonzero dose of investigational drug is administered and recorded on DAR (e)CRF. The date of last administration of investigational drug will also be referred as the last date of investigational drug.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, ▮ etc) is the start date of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25. A week length is 7 days. If duration is reported in weeks, duration in days will be divided by 7.

Baseline

For **non-efficacy assessments, Baseline** is the last available and valid assessment performed or value measured within 21 days before the first administration of study treatment, 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., ECG, ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮).

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 CSP, it should be performed before the first treatment administration.

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

The baseline ECG interval value will be obtained by averaging each of the ECGs available before the first dose of BGJ398 up to 21 days before the first dose of investigational drug.

For **efficacy assessments**, **Baseline** is defined as:

Non Surgery Group: baseline scan must occur within 28 days after the initiation of study treatment.

Surgery Group: an MRI scan, performed within 72 hours after surgery, can function as the baseline scan if BGJ398 therapy is initiated within 4 weeks of surgery. If BGJ398 is initiated after 4 weeks following surgery, a baseline scan must be performed within 7 days of starting BGJ398.

On-treatment assessment/event and observation periods

For adverse event reporting 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 administration of study treatment

2. *on-treatment period*: from date of first administration of study treatment to 30 days after date of last actual administration of study.

3. *post-treatment period*: starting at day 30+1 after last administration of study treatment.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

Windows for multiple assessments

In order to summarize ECOG performance status, ▮ vital signs, and other data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for assessments

Assessment	Target day of assessment	Time Interval
Baseline		≤ Day 1
Cycle 1 Day 15	15	Day 2 to day 21
Cycle 2 Day 1	29	Day 22 to day 42
Cycle 3 Day 1	57	Day 43 to day 63
Cycle 3 Day 15	71	Day 64 to day 77
Cycle 4 Day 1	85	Day 78 to day 98
Cycle k Day 1 (k≥5)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-2 Last contact date data sources

Source data	Conditions
Last contact date/last date patient was known to be alive from Survival Follow-up page	- Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.

Source data	Conditions
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
RANO assessment date	Evaluation is marked as 'done'.
Laboratory ▮ collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' (e)CRF.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Treatment group will be named as: Non Surg BGJ398 125 mg and Surg BGJ398 125 mg. If there are no patients in the surgery group, only Non Surg BGJ398 125 mg will be presented.

Full Analysis Set

The Full Analysis Set (FAS) includes all patients who received at least one dose of BGJ398. The FAS will be used for all listings of raw data. Unless otherwise specified the FAS will be the default analysis set used for all analyses.

Per protocol set (PPS)

The Per-Protocol Set (PPS) will consist of a subset of patients in the FAS (with FGFR1-TACC1, FGFR3-TACC3 and/or activating mutations in FGFR1, 2 or 3) who are compliant with requirements of the CSP. The PPS will include patients who have an adequate tumor assessment at baseline, a follow-up tumor assessment >8 weeks after starting treatment unless disease progression is observed before that time, and no protocol deviations.

Safety

The Safety Set includes all patients who received at least one dose of BGJ398 and have at least one valid post-baseline safety assessment.

The statement that a patient had no AE (on the AE (e)CRF) constitutes a valid safety assessment.

The treatment received is defined as:

- The treatment assigned if it was received at least once, or
- The first treatment received when starting therapy with study treatment if the assigned treatment was never received.
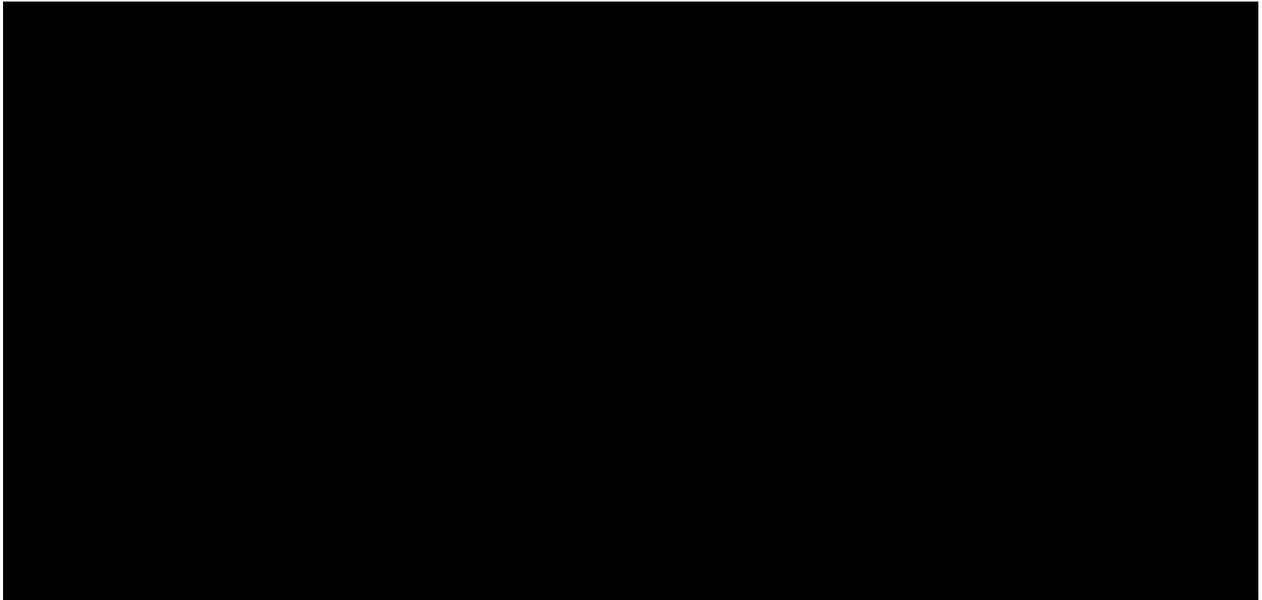
Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-3.

Table 2-3   Determination of analysis set membership

Description used to report Protocol Deviations	Protocol deviation IDs	Analysis set(s) to be excluded
Inclusion criteria not met	INC01, INC02, INC04	PPS
Use of prohibited concomitant medication	WITH04, WITH05, TRT05	PPS

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the (e)CRF.

2.3   Patient disposition, demographics, disease history and medical history

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data, e.g. gender, age groups: <65 and $\geq$ 65 years, race, ECOG performance status, FGFR status (FGFR1/2/3 Amplified/Mutated/Translocated), will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data, e.g. age, weight, height, body mass index, will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). BMI (kg/m2) will be calculated as weight[kg] / (height[m]2) using weight at Baseline.

Diagnosis and extent of cancer (disease history)

Diagnosis and extent of cancer will be tabulated for primary site of cancer, details of tumor histology/cytology and histological grade.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e)CRF will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version 20.1used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

2.3.1   Patient disposition

The following patient disposition information will be summarized for patients in the FAS:

- Enrolled patients who remained on treatment or discontinued treatment, based on the end of treatment (e)CRF (note that patients remained on treatment if the last known date the patient took study drug is later than the cut-off date)
- Primary reasons for end of treatment (EOT).
- Number (%) of patients who are discontinued and have entered the 30 day safety follow-up (based on the 'End of Treatment Phase Completion' page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Phase Completion' page).
- Primary reasons for end of study

A listing of EOT details will be produced. Patients enrolled but not treated will be listed along with the reason for discontinuing from the study. Additionally, a listing of screen failure

patients, with reason for screen failure will be produced. Since screening failures are not part of any analysis sets, they will not be included in any of the summary tables.

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan). Protocol deviations leading to exclusion from analysis sets will be tabulated separately. All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual dose intensity (ADI) and relative dose intensity (RDI) will be summarized. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

The duration of exposure is calculated as detailed below.

For patients who discontinued permanently from the study as of the data cut-off date:

Duration of exposure (days) = (end date of study drug + X) – (start date of study drug) + 1,

where study drug is BGJ398 and X is the number of days from last administered dose to the next planned dose taking into account the minimal allowed dosing interval. If the last dose of a cycle was taken later than the scheduled cycle length (28 days), X will be set to 0 days. For BGJ398, X equals to 0 if the cycle day of the last dose is less than 21 days; otherwise, X equals to (28 – cycle day of the last dose).

For patients who are still on-treatment as of data cut-off date:

Duration of exposure (days) = data cut-off date – (start date of study drug) + 1.

Summary of duration of exposure of study treatment in weeks will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc.). Duration of exposure will be categorized into time intervals (i.e. < 4 weeks, 4 - < 8 weeks, 8 - < 12 weeks, 12 - < 16 weeks, 16 - < 24 weeks, 24 - < 32 weeks and >= 32 weeks); frequency counts and percentages will be presented for the number (%) of subjects in each interval.

Exposure will be summarized on the Safety Set.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the DAR (e)CRF.

For patients who did not take any drug the cumulative dose is by definition equal to zero.

Relative dose intensity

Actual dose intensity (ADI) for patients with non-zero duration of exposure is defined as follows:

ADI (*mg / day*) = Actual Cumulative dose (*mg*) / Duration of exposure to study treatment (*day*).

For patients who did not take any drug the ADI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (*mg / day)* = Planned Cumulative dose (*mg*) / Duration of exposure (*day*).

Relative dose intensity (RDI) is defined as follows:

RDI = ADI (*mg / day*) / PDI (*mg / day*).

Dose reductions, interruptions or permanent discontinuations

The number of subjects who have dose reductions, dose interruptions, or dose permanent discontinuations, and the reasons, will be summarized. 'Dose Changed', 'Dose interrupted', and 'Dose permanently discontinued' fields from the DAR (e)CRF will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively. **Note**: planned 1 week off in dosing schedule will not be collected or counted as dose interruption. The corresponding field 'Reason' for dose changed, dose interrupted, and dose permanently discontinued will be used to summarize the reasons.

A dose reduction is defined as a decrease in total daily dose from the protocol planned dose, and a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption, and the dose change flag is checked. For example, in the sequence 125 mg – 0 mg – 100 mg, the 100 mg dose will be counted as a reduction.

A dose interruption is defined as an instance that no study drug (0 mg) is taken when the protocol planned dose is non-zero. For example, in the sequence 125 mg – 0 mg – 100 mg, the 0 mg dose will be counted as an interruption.

2.4.2   Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized. For prior medications. Summaries will include prior antineoplastic regimens, total number of regimens, setting at last treatment based on end date, best response at last treatment based on end date. For prior radiotherapy, locations and setting at last radiotherapy will be summarized. For prior surgery, procedure at last surgery (biopsy or other) and residual disease will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

The above analyses will be performed using the FAS.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy includes medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and

2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

2.5   Analysis of the primary objective

The primary objective of the study is to assess the anti-tumor activity of BGJ398 for patients with GBM and/or other glioma subtypes with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, 2 or 3.

2.5.1   Primary endpoint

PFS rate at 6 months (PFS6) as defined by RANO criteria assessed by the investigator will be the primary endpoint.

Non Surgery Group: PFS is defined as the number of days from the first day of treatment to the date of the first documented disease progression or date of death, whichever occurs first.

Surgery Group: PFS is defined as the number of days from the first day of treatment after surgery to the date of the first documented disease progression or date of death, whichever occurs first.

2.5.2   Statistical hypothesis, model, and method of analysis

A Bayesian design will be used in order to estimate the PFS6 rate and to provide inferential statements based on the uncertainty of this quantity. Progression free survival will be modeled using a Weibull distribution. The Weibull distribution is a flexible distribution which allows for time varying hazard rate. The probability density function is given by $f(x) = \upsilon\lambda x^{(\upsilon-1)}\exp(-\lambda x^{\upsilon})$ where υ is a shape parameter and λ a scale parameter. Prior distributions will be placed on both parameters to carry out the analysis. For the scale parameter, a normal (mean = 0, standard deviation = 2.236) distribution will be used on the log of the parameter. For the shape parameter, an exponential with rate 1 will be used. These priors correspond to a prior probability of unacceptable efficacy (PFS6 <16%) of 65 %, and clinically relevant efficacy (PFS6 > 40%) of 25% (see Figure 2-1 below).

Figure 2-1   PFS6 prior distribution
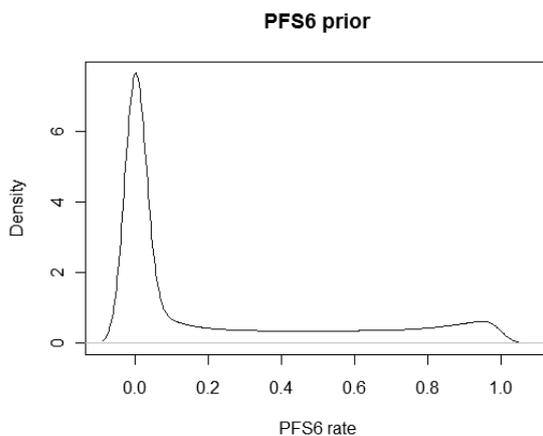
The posterior distributions will be updated with all the data available at the time of the analyses from the patients in the PPS who are evaluable for the primary analysis. Once updated, the posterior probability that the true PFS6 rate at the dose of BGJ398 used in the study lies in the following categories will be summarized:

[0, 16%) unacceptable efficacy

[16%, 25%) limited efficacy

[25%, 40%) moderate efficacy

[40%, 100%] clinically relevant efficacy

Data from both the treatment groups will be pooled together for this analysis, since we expect to observe similar 6-month PFS rates for these two groups. The study will be considered a success at the final analysis if

- there is at least 50% confidence that BGJ398 has clinically relevant efficacy (that is, Post Prob(PFS6>=40%) > 50%), and

- there is at least 80% confidence that BGJ398 has either moderate efficacy or clinically relevant efficacy (Post Prob(PFS6>=25%) > 80%).

2.5.3   Handling of missing values/censoring/discontinuations

Patients who discontinue the study and are lost to follow-up without a known date of progression or death due to any cause on or before the cut-off date will be censored in the primary analysis at the date of their last available tumor assessment.

2.5.4   Supportive analyses

As a supportive analysis, Kaplan-Meier estimates of the PFS rate at 4, 6,12, 16, 18 and 24 months, $25^{th}/75^{th}$ percentile and median PFSwill be derived together with 95% confidence intervals. PFS will also be presented descriptively using Kaplan Meier plots. This analysis will be done with all patients in both the treatment groups pooled together.

2.6   Analysis of the key secondary objective

Not applicable.

2.7   Analysis of secondary efficacy objective(s)

The secondary objectives of the study is to assess the anti-tumor activity of BGJ398 based on objective response rate and overall survival using RANO criteria.

Each patient will be evaluated for all potential sites of tumor lesions at Screening and every 8 weeks after starting study treatment until disease progression.

On-study tumor assessments have a ± 7 day window, except for the first post-baseline tumor assessment and for confirmatory scans (4 weeks +7 day window only). The first post-baseline tumor assessment should be performed on day 1 of cycle 3 (+7 day window permitted) after starting treatment. There will be a tumor assessment at the End of Treatment (+ 7 days) if the patient discontinues for any reason other than disease progression and the last tumor assessment has been performed > 28 days prior to this day.

2.7.1   Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients with a best overall response of Complete Response (CR) or Partial Response (PR), as per the RANO criteria.

The ORR analysis will include patients from the FAS who have measurable disease (as per RANO) at their baseline scan. ORR will be reported with 95% confidence interval and response will be listed.

This analysis will be done for all patients in the PPS as well as the FAS in both treatment groups pooled together.

2.7.2   Overall Survival

Non-Surgery Group: overall survival (OS) is defined as the time from the date of start of treatment to the date of death due to any cause or the date of last contact (censored observation) at the date of data cutoff.

Surgery Group: OS is defined as the number of days from the first day of treatment after surgery to the date of death due to any cause or the date of last contact (censored observation) at the date of data cutoff. If the patient does not receive at least one post-surgical dose of BGJ398 (i.e., C1D1), the patient will be excluded from the overall survival analysis.

The survival time for patients without documentation of death prior to analysis data cutoff, will be censored at the last date the patient was known to be alive prior to the cutoff date. Survival time for patients with no post-baseline survival information will be censored on the date of start of treatment.

OS will be analyzed using the Kaplan-Meier method. Survival rate at 4, 6, 8, 12, 18 and 24 months and median OS will be estimated along with 95% confidence intervals.

This analysis will be done for all patients in the PPS as well as the FAS in both treatment groups pooled together.

2.8   Safety analyses

A secondary objective of the study is to characterize the safety and tolerability of BGJ398.

The assessment of safety is based on the frequency and severity of AEs and SAEs, changes in hematology and chemistry values, specifically those associated with calcium/phosphate homeostasis and renal function, and on the number of laboratory values that fall outside of pre-determined ranges (CTCAE v 4.03 grading limits or normal ranges as appropriate). Other safety (e.g., ECGs, vital signs and special tests, e.g. pregnancy test) analyses will be considered as appropriate.

All safety analyses will be based on the safety set.

The safety summary tables will include only on-treatment assessments. All safety assessments will be listed, and those collected later than 30 days after study treatment discontinuation will be flagged.

2.8.1   Adverse events (AEs)

AE summaries

AEs will be coded using MedDRA terminology, the latest version which will be available at the time of analysis.

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE

relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency.

The following adverse event summaries will be produced:

- Overview of adverse events and deaths (number and % of subjects who died, with any AE, any SAE, any dose reductions/interruptions, AE leading to discontinuation);
- AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment);
- Seriousness (SAEs and non-SAEs);
- Leading to treatment discontinuation;

The following listings will be produced:

- All adverse events (safety set)
- Adverse events among subjects who were not treated (all screened subjects)

Deaths

- Summaries for on-treatment and all deaths (including post-treatment death) will be produced by system organ class and preferred term.

- All deaths will be listed for the safety set, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.8.2   Laboratory data

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listing of all CTC grade 3 or 4 laboratory toxicities

Table 2-4 lists those entire laboratory parameters for which CTCAE grades are defined, Table 2-5 lists the remaining laboratory parameters for which shift tables were based upon the local lab normal range.

Table 2-4 Laboratory parameters to be presented in grade shift tables based on CTC grade

Hematology	Biochemistry	Coagulation
White blood cell count (WBC)	AST (SGOT)	Fibrinogen
Hemoglobin	ALT (SGPT)	PT
Platelets counts	Total Bilirubin	PTINR
Abs. Neutrophils	Albumin	PTT
Abs. Lymphocytes	Creatinine	
	Alkaline Phosphatase	
	Glucose	
	Calcium	
	Sodium	
	Magnesium	
	Potassium	
	Hypophosphatemia	

ALT (SGPT) = Alanine aminotransferase/glutamic pyruvic transaminase; AST (SGOT) = Aspartate aminotransferase/glutamic oxaloacetic transaminase; PT = prothrombin time; PTINR = prothrombin time International normalized ratio

Table 2-5   Laboratory parameters to be presented in shift tables based on local lab normal ranges

Hematology	Biochemistry	Coagulation
Absolute eosinophils	BUN	
Absolute basophils	Total protein	
Absolute monocytes	Direct bilirubin	
Red blood cell count (RBC)	LDH	
Hematocrit (HCRIT)		

2.8.3   ECOG performance status

Frequencies and percentages for the categories of the ECOG performance scale will be listed.

Table 2-6   ECOG performance status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Note: Grade 5 (dead) was removed from this table. This information will be collected on a separate (e)CRF page.

2.8.4   Other safety data

2.8.4.1   ECG and cardiac imaging data

12-lead ECGs including PR, QRS, QT, and QTcF, will be obtained central/local for each subject during the study. ECG data will be read and interpreted centrally locally

The number and percentage of subjects with notable ECG values will be presented.

- QT, or QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline $>25\%$ and to a value > 100 bpm

- Decrease from baseline >25% and to a value < 50 bpm
- PR
    - Increase from baseline >25% and to a value > 200 ms
    - New value of > 200 ms
- QRS
    - Increase from baseline >25% and to a value > 120 ms
- New values of QRS > 120 ms

A listing of notable ECG values will be produced. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.4.2   Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-7 below.

Table 2-7   Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	-

The number and percentage of subjects with notable vital sign values (high/low) will be presented.

A listing of notable vital values will be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.
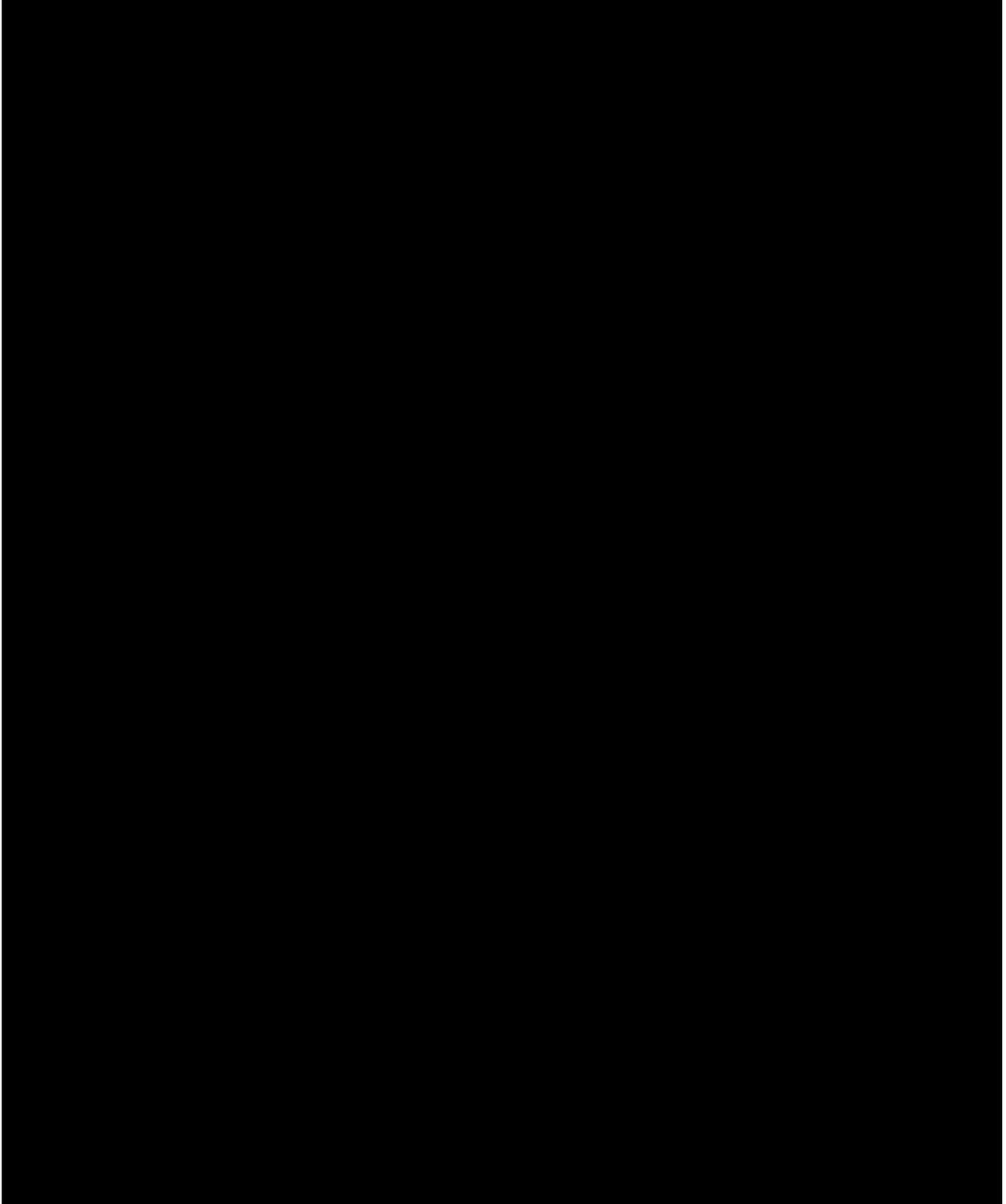
2.11 Interim analysis

Not applicable.

3 Sample size calculation

The operating characteristics of the design have been assessed via simulations (see Table 3-1below). For each scenario, 1000 trials were simulated. A scenario was defined by assumption regarding the true PFS6 rate, an accrual rate of one patient per month with the final analysis taking place after the last patient completed 6 cycles of treatment or discontinued. A success was defined as follows:

Prob (PFS6 > 25%) > 80% and Prob (PFS6 > 40%) > 50% at the final analysis.

Table 3-1   Operating characteristics of study design

	True PFS6					
	0.16	**0.25**	**0.35**	**0.4**	**0.45**	**0.5**
Prob. of stopping at interim	0.870	0.506	0.165	0.082	0.035	0.014
Average sample size	21.589	27.016	31.799	32.922	33.547	33.822
Prob. of success (final)	0.000	0.003	0.227	0.488	0.746	0.917
Average study duration (months)	20.674	27.388	33.650	35.269	36.261	36.807

Assuming a true PFS6 rate of 50% and a uniform accrual of one patient per month, with 34 patients in total (~27 PFS events), there is about 92% chance to achieve success at the end of the study.

4 Change to protocol specified analyses

Interim analysis is planned in the CSP: an interim analysis for futility was planned to be carried out once 10 patients in the PPS have completed 6 cycles of treatment or discontinued earlier. No actual interim analysis was performed.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 1 should not applicable for final CSR. All patients should have EOT page complete before the Database lock for Final CSR

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Please note that date of assessment on EOT CRT might be very different from last date of dose.

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

> **Use Dec31yyyy**

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

> **Use EOT date**

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

> **Use last day of the Month (mm)**

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

> **Use the treatment start date**

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2   AE, ConMeds and safety assessment date imputation

Table 5-1   Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	     ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	     ○ Else set start date = study treatment start date.
	 • If available year > year of study treatment start date then 01JanYYYY
	 • If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule

day	• If available month and year = month and year of study treatment start date then
	    o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	    o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2   Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications.

5.1.2.1   Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date, then the evaluation is considered post-cut-off date and will be excluded from analysis.

Prior anti-neoplastic therapy

No imputation of therapy start or end date will be done.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

6 Reference

Clinical trial Protocol CBGJ398X2201

████████ Developing and Completing the Clinical Study Report