NOVARTIS

Clinical Development

BGJ398

Protocol CBGJ398X2201 / NCT01975701

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

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List of abbreviations

AE	Adverse Event
ALT/SGPT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolutely Neutrophil Count
AST/SOPT	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC_{0-24}	Area Under the Curve 0-24 h
BCRP	Breast Cancer Resistance Protein
BLRM	Bayesian logistic regression model
BSL	Baseline
BUN	Blood Urea Nitrogen
Ca	Calcium
CL	Clearance
C_{max}	Maximum Concentration
C_{min}	Minimum Concentration
CNS	Central Nervous System
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	Central Serous Retinopathy
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
CTL	Clinical Trial Lead
CYP	Cytochrome P
DCE-MRI	Dynamic contrast enhanced - magnetic resonance imaging
DDS	Dose-determining set
DHEA	Dehydroepiandrosterone
DLT	Dose limiting toxicity
[redacted]	[redacted]
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report/Record Form
EGFR	Epidermal growth factor receptor
EIAED	Enzyme induced anti-epileptic drug
EOT	End of Treatment
EU	European Union
F	Bioavailability
FAS	Full Analysis Set
FFPE	Formalin-fixed paraffin-embedded
FGF	Fibroblast growth factor
FGFR	Fibroblast Growth Factor receptor
FLT1	Fms-related tyrosine kinase 1
FSH	Follicle-stimulating hormone
GBM	Glioblastoma

GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
HbA_{1c}	Glycosylated Hemoglobin
hCG	human chorionic gonadotrophin
hERG	Human *Ether-à-go-go*-Related Gene
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
IB	Investigators Brochure
IC_{50}	Half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International Normalized Ratio
IOP	Intraocular pressure
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLN	Lower limit of Normal
LLOQ	Lower Limit of Quantification
LPLT	Last patient last treatment
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
MRP-2	Multidrug-Resistance Related Protein
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated acquisition scan
N	Sample size
NA	Not applicable
NYHA	New York Heart Association
OC	Oral contraception
OCT 2	Organic cation transporter-2
ORR	Objective Response Rate
OS	Overall survival
p.o.	*per os*/by mouth/orally
[redacted]	[redacted]
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PDGFR	Platelet-derived growth factor receptors
PFS	Progression-free survival
PFS6	Progression-free survival at 6 months
P-gp	P-glycoprotein
Pi	Inorganic phosphorous
PI3K	Phosphatidylinositol-3-kinase
PI3KCA	phosphatidyl inositol 3-kinase catalytic subunit
PK	Pharmacokinetics

PPS	Per protocol set
PR	Partial Response
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
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
RNA	Ribonucleic Acid
RP2D	Recommended Phase II dose
RT	Radiation therapy
SAE	Serious Adverse Event
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoC	Standard of Care Treatment
STD_{10}	Severely toxic dose in 10%
TACC	Transforming acidic coiled-coil
TdP	Torsades de Pointes
t_{max}	The time at which the maximum observed concentration (C_{max}) occurs
TMZ	Temozolomide
U.S. FDA	the U.S. Food and Drug Administration
ULN	Upper Limit of Normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
V_{ss}	Volume of distribution at steady state
VTE	Venous thromboembolism
WBC	White Blood Cell

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.,:q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug”.
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study group administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendment 2

Amendment rationale

- The purpose for this amendment is as follows:Recent clinical data shows that FGFR amplification is a poor surrogate for fusion presence and that patients identified with FGFR-TACC fusions in GBMs and other gliomas show radiological evidence of response when treated with FGFR inhibitors (Di Stefano et al, 2015). For this reason the Inclusion/Exclusion criteria were modified to exclude patients with FGFR1, 2, 3, and 4 amplifications and to include GBM and/or other glioma subtype patients with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutations in FGFR1, 2 or 3 gene.
- Following feedback from study investigators, and in order to ensure that patients who could potentially benefit from the trial are not excluded, the upper limit of two chemotherapy regimens prior to study entry was removed.
- The safety information was updated as per the latest information in the Investigator Brochure.
- Hyperphosphatemia management guidelines were updated to provide more detail regarding the prophylaxis of hyperphosphatemia and how to modify BGJ398 dose administration in response to elevated serum phosphorus levels.
- Serum creatinine and creatinine clearance exclusion criteria were revised to align with current medical practice and provide consistency across BGJ398 protocols. BGJ398 has not been demonstrated to be nephrotoxic.
- The criteria for drug discontinuation due to asymptomatic increase in lipase have been relaxed. Asymptomatic mild to moderate increases in lipase have been seen with BGJ398 dosing, particularly in patients with cholangiocarcinoma, but there have been no cases of pancreatitis.
- The frequency of ophthalmological assessments was reduced to align with other BGJ398 protocols.
- The statistical methods and data analysis section was revised based on the changes to the inclusion criteria.
- The list of concomitant medications was revised based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: 29 Oct 2012)

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes to the protocol have been made:

- Updated Protocol Summary with the revisions to inclusion criteria regarding the inclusion of patients with GBM and/or other glioma subtype patients with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, 2 or 3. The number of allowed prior chemotherapy regimens was revised from two to unlimited. Reference to amplification or translocation was removed throughout the protocol.

- Section 1.1 (Background) was updated to include background information and rationale on inclusion of patients with other glioma subtypes. In addition, the rationale was provided on why FGFR amplification is a poor surrogate to detect FGFR fusions.
- Section 1.2.1.2 (Clinical experience) was updated with the most recent information as per latest version of the Investigator Brochure.
- Section 2 (Rationale) was updated with the additional rationale for treating glioma patients with FGFR inhibitor.
- Section 3 (Objectives and endpoints), Section 4 (Study design), Section 5 (Population) was updated to reflect the revisions to the study inclusion criteria.
- Section 5.2 (Inclusion criteria) inclusion criteria # 1, 3 and 6 were revised to reflect the changes in study inclusion criteria.
- Section 5.3 (Exclusion criteria) exclusion criteria # 17 and 19 were revised to reflect the changes in study exclusion criteria.
- Section 6.2 (Dose modifications) was revised to update the management of hyperphosphatemia, renal toxicities, asymptomatic amylase and/or lipase elevation
- Section 6.3 (Concomitant medications) was updated to provide the latest recommendation on the management of the hyperphosphatemia.
- Section 7.1 (Study flow and visit schedule) was updated with the reduced frequency of ophthalmologic assessments.
- Section 7.1.1 (Molecular pre-screening) was updated with the number of required slides for molecular pre-screening.
- Section 10 (Statistical analysis) was revised based on the updated inclusion criteria.
- Appendix 1 and Appendix 2 (List of concomitant medications) was revised.

IRB/IEC/HA

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1

Amendment rationale

This amendment addresses changes requested following health authority review, and includes the following:

- The protocol exclusion criteria has been updated to indicate that patients with current evidence of corneal/keratopathy or retinal disorder are not eligible to participate. This update is being performed to align with the BGJ398 Investigator's Brochure (edition 6).
- The protocol will be updated to include ophthalmologic eye exam assessments in order to assess for early signs of corneal or retinal changes at baseline and monitor at periodic intervals. This update is being performed to completely align with the BGJ398 Investigator's Brochure (edition 6).
- The protocol will be updated to exclude patients with clinically significant hypokalemia. Clinically significant hypokalemia is known to increase the risk of dysfunction of ion channels in the myocardial cell membrane and therefore may increase the risk of TdP tachycardia.
- The protocol has specified a recovery period of at least 2 weeks following surgery before patients can receive BGJ398 treatment for patients enrolled in Group 2 (surgical group).

Also in this amendment, other sections have been modified for consistency and/or clarification, such as management of hyperphosphatemia.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes to the protocol have been made:

- Sections 2.2 (Rationale for the study design) and 4.1 (Description of study design): Included a minimum of 2 weeks following surgery before patients can resume and receive BGJ398 treatment for patients enrolled in Group 2 (surgical group).
- Section 5.2 (Inclusion Criteria #11): Changed grading of recovery from adverse events of previous systemic anti-cancer therapies from grade 1 to grade 2.
- Section 5.2 (Inclusion Criteria #7): Clarified that patients who had recent surgery and have no evidence of disease, the surgery should within 6 weeks of first dose.
- Section 5.3 (Exclusion Criteria #3): Updated stable dose of steroid criteria from at least 2 weeks to 1 week and clarified local application or prophylactic use of steroid is allowed.
- Section 5.3 (Exclusion Criteria #17): Patients with Gilbert's Syndrome must not have bilirubin $\geq$ 2.5 ULN, not $\geq$ 1.5 ULN. This typographical error is corrected.
- Section 5.3 (Exclusion Criteria #18): (1) Clarified that it is the outside upper limit of normal level of serum inorganic phosphorus or calcium as the criteria for exclusion. (2) Clarified either serum total or ionized calcium level is measured to assess calcium-phosphate homeostasis
- Section 5.3 (Exclusion Criteria #19): Included clinically significant hypokalemia as part of criteria of cardiac disease.

- Section 5.3 (Exclusion Criteria #23): Added patients with current evidence of corneal/keratopathy or retinal disorder as part of exclusion criteria.
- Table 6-3 (Criteria for interruption and re-initiation of BGJ398 treatment for hyperphosphatemia): Clarified the instructions of management of hyperphosphatemia.
- Table 6-4 (Follow-up for study drug induced toxicities for hyperphosphatemia): Updated table to reference Table 6-3 for management of hyperphosphatemia and Section 6.3.1 for taking oral phosphate binders as prophylactic therapy.
- Section 6.3.1 (Permitted concomitant therapy): Inserted text paragraph that oral phosphate binders such as Sevelamer are allowed and should be taken with the first day of BGJ398 therapy.
- Table 7-1 (Visit evaluation schedule): Added schedule for ophthalmologic eye examinations.
- Section 7.2.2.7.1 (Electrocardiogram): (1) Clarified that the QTcF value must be within eligibility criteria prior to study drug treatment for ECG collected on Cycle 1 Day 1 pre-dose. (2) Corrected QTcF value from ≥ 501 to ≥ 500 ms.
- Section 7.2.2.8 (Ophthalmologic assessments): Added ophthalmologic eye examination assessments for safety monitoring.

- Section 8.6 (Data Monitoring Committee): Clarified the formal interim analysis plan.

IRB/IEC/HA

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	BGJ398X2201
Title	A Phase 2, multicenter, open-label study of BGJ398 in patients with recurrent resectable or unresectable Glioblastoma
Brief title	A phase 2 study of BGJ398 in patients with recurrent GBM
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Glioblastoma (GBM) is a highly malignant brain tumor of astrocytic origin accounting for over 50% of all gliomas. Recently Singh et al. (Singh et al, 2012) reported that a small subset of GBMs (3.1%) harbors oncogenic chromosomal translocations that fuse in-frame the tyrosine kinase coding domains of fibroblast growth factor receptor (FGFR) genes (FGFR1 or FGFR3) to the transforming acidic coiled-coil (TACC) coding domains of TACC1 or TACC3, respectively. There is a high unmet medical need for GBM patients: ● the median OS is approximately 18 months ● there are 10,000 new cases per year in US ● annual incidence rate of 3 to 4 cases per 100,000 persons, resulting in 240,000 new cases worldwide each year ● virtually all patients experience recurrence and therapeutic options have limited benefit. Treatment options are: ● Surgery/RT/temozolomide is the standard of care for newly diagnosed patients, which leads to an increase in median OS from 12.1 to 14.6 months ● Therapy for recurrent disease includes surgery, RT, bevacizumab, chemotherapy, which leads to a historical median OS of 30 weeks Lentivectors expressing FGFR-TACC fusions injected directly into short term astrocytic cell cultures as well as the brain parenchyma of mice have been shown to fully recapitulate GBM. FGFR-TACC induced GBM (and derived cell lines) were successfully treated with FGFR inhibitors such as BGJ398. Recent clinical data shows that FGFR amplification is a poor surrogate for fusion presence and that patients identified with FGFR-TACC fusions in GBMs and other gliomas show radiological evidence of response when treated with FGFR inhibitors (Di Stefano et al, 2015). Therefore, FGFR-TACC fusions could potentially identify a subset of GBM and other gliomas patients who would benefit from targeted FGFR kinase inhibition.
Primary Objective(s) and Key Secondary Objective	To assess the anti-tumor activity of BGJ398 in patients with GBM and/or other glioma subtypes with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1,2or 3 based on PFS6
Secondary Objectives	To further assess the anti-tumor activity of BGJ398 in 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 To further assess the anti-tumor activity of BGJ398 in patients with GBM and/or other glioma subtypes with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1,2or 3 based on OS To characterize the safety and tolerability of BGJ398
Primary endpoints	PFS rate at 6 months as defined by RANO criteria as assessed by the investigator

Secondary Endpoints	ORR (patients with measurable disease) as defined by RANO criteria (Appendix 3) as assessed by the investigator Overall survival (OS) Safety: type, frequency, and severity of AEs and SAEs Tolerability: dose interruptions, reductions and dose intensity, and evaluations of laboratory values
Study design	This is an open-label non-randomized, multicenter, phase II study of BGJ398 administered to patients with recurrent GBM and/or other glioma subtypes, whose tumors demonstrate FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, 2 or 3. . Patients will be enrolled in two groups. Group 1 will enroll patients who are not candidates for surgery. Patients in group 1 will receive BGJ398 on a three week on, one week off schedule. Group 2 will enroll patients who are surgical candidates. Patients in group 2 will receive BGJ398 for 5-10 days prior to surgery and will continue to receive BGJ398 on a three week on, one week off schedule, at a minimum of 2 weeks and no more than 6 weeks following surgery. [redacted] Patients from both groups will be evaluated for tumor response and progression by Gd-enhanced MRI every 8 weeks until disease progression or discontinuation from study using RANO criteria.
Population	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.
Inclusion criteria	Patients eligible for inclusion in this study have to meet all of the following criteria: 1. Patients with histologically confirmed GBM and/or other glioma subtypes at the time of diagnosis or prior relapse. Note that all subtypes of gliomas are permitted. Any question of eligibility should be discussed with Novartis. 2. At least 15 to 20 unstained slides and/or a tumor block from at least one prior surgery must be available for molecular testing, unless agreed otherwise upon between Novartis and the Investigator. 3. Written documentation of local or central laboratory determination of FGFR1-TACC1, and/or FGFR3-TACC3 fusion and/or activating mutation in FGFR1, FGFR2 or FGFR3 is required. Patients identified to have an activating mutation in FGFR1,2or 3 may be eligible pending agreement between Novartis and Investigator 4. RANO defined tumor progression by MRI in comparison to a prior scan; OR, progression that does not meet RANO criteria if the disease progression is otherwise obvious in the opinion of the investigator and is discussed with the Novartis; OR histologically proven recurrent/progressive disease based on histology if surgery was the treatment for the most recent progression. 5. Patients must have received prior external beam radiotherapy and temozolomide. 6. Unlimited prior surgeries and chemotherapies are permitted. 7. Group specific inclusion: ● **Group 1**: RANO defined tumor progression as per Inclusion Criteria 4. Additionally, patients who recently underwent resection for RANO defined tumor progression and are post-operative without evidence of RANO tumor progression may also be eligible for Group 1 assuming all inclusion/exclusion criteria are met and the most recent surgery has occurred within six weeks of the planned first treatment dose. ● **Group 2**: RANO defined tumor progression as per Inclusion Criteria 4 and planned surgical resection. Additionally, if a patient assigned to Group 2 does not undergo planned surgical resection, then the patient will be allowed to continue therapy as per Group 1. If a patient enrolled to Group 2 needs to undergo surgical resection sooner than initially planned (and having had less

	than 5 days of BGJ398), then the patient will still be allowed to continue therapy post-surgically as per Group 2 regardless of the number of days the patient received BGJ398 pre-surgically.
Exclusion criteria	Patients eligible for this study must not meet any of the following criteria prior to the first treatment. 1. History of another primary malignancy except: in situ carcinoma of any-type that has been adequately treated; or non-melanoma carcinoma of the skin; or any other curatively treated malignancy that has not been treated in the prior 3 months or expected to require treatment for recurrence during the course of the study; or any indolent malignancy that has not required treatment within the prior 2 years (even if never previously treated). 2. Prior or current treatment with a FGFR inhibitor (unless agreed otherwise between Novartis and the Investigator on a case by case basis). 3. Neurological symptoms related to underlying disease requiring increasing doses of corticosteroids. **Note***:* Steroid use for management of CNS tumors is allowed but must be at a stable dose for at least 1 week preceding the baseline MRI/CT. If the corticosteroid dose is increased between the date of imaging and the initiation of study treatment, a new baseline MRI/CT is required. Definition of stable steroids includes patients on no steroids. Local administration methods or prophylactic use is allowed. 4. Patients must not be taking Enzyme Inducing Anti-Epileptic Drug (EIAED) (Refer to Appendix 2 for list of prohibited medications). If previously on an EIAED, the patient must be off of it for at least two weeks prior to study treatment.
Investigational and reference therapy	BGJ398, 125 mg p.o. q.d., 28 day cycle duration, 3 weeks on, 1 week off schedule
Efficacy assessments	Tumor response per RANO criteria; 6 month Progression Free Survival (PFS) rate, Overall Response Rate (ORR) and Overall Survival (OS)
Safety assessments	● Physical examinations ● Vital signs ● Laboratory evaluations ● Radiological examinations ● Cardiac assessments ● Ophthalmologic examinations
[redacted]	

Data 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. An interim analysis for futility will be carried out once 17 patients in total for both groups have completed 6 cycles of treatment or discontinued earlier. ORR will be reported together with a two-sided 95% confidence interval. OS will be analyzed using the Kaplan-Meier method. All the data will be summarized with respect to demographic, baseline characteristics and safety observations using descriptive statistics (quantitative data) and contingency tables (qualitative data). The study data will be analyzed and reported based on patients from the pooled group 1 and group 2. Details of the statistical analysis and data reporting will be provided in Novartis Report and Analysis Plan.
Key words	BGJ398, recurrent GBM, activating mutation in FGFR 1, 2 or 3 gene, FGFR1-TACC1, FGFR3-TACC3

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Glioblastoma (GBM) is a highly malignant brain tumor of astrocytic origin which accounts for over 50% of all gliomas. GBM has an annual incidence rate of 3 to 4 cases per 100,000 people resulting in 240,000 newly diagnosed cases worldwide each year (CBTRUS 2012; Ferlay et al, 2008).

The current standard treatment for GBM is surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide (TMZ). For newly diagnosed GBM, the addition of TMZ to surgery and radiation therapy prolongs median survival (from 12.1 to 14.6 months) and increases the five-year survival rate (from 2% to 10%; hazard ratio 0.63; 95% CI 0.53-0.75; p<0.0001) (Stupp et al, 2009).

However, at recurrence, no cytotoxic or targeted therapeutic has improved the 6-month-PFS rate of 10-20%, a median overall survival of 6-9 months, and an average 5 year overall survival of 3.3% (Stupp et al, 2006; Wong et al, 1999; Lamborn et al, 2008; Wong et al, 2011; Hofer et al, 2011; Wen et al, 2009; Norden et al, 2008; Yung et al, 2000) with the possible exception of bevacizumab.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), was approved in the US for the treatment of recurrent GBM based on a clinically meaningful and durable objective tumor response rate (ORR 28%-38%, median duration of response 4.2 months). The 6-month-PFS rate in the multiple studies ranged from approximately 29% to 50% and represented a significant improvement over the historical 10-20% 6-month-PFS rate. Despite the improvement in response provided by bevacizumab, most patients with GBM experience relapse within months (Friedman et al, 2009; Kreisl et al, 2009) and options for salvage remain extremely limited.

Genetically, GBM is characterized by complex chromosomal abnormalities and extensive intratumor cytogenetic and histological heterogeneity displaying the genetic alterations that govern the processes of cellular proliferation, survival, invasion and angiogenesis (TCGA 2008; Harada et al, 2000; Walker et al, 2001). Common mutations found in GBM include: EGFR overexpression (70%) (Maher et al, 2006); TP53, RB, INK4a, PDGF-R, VEGF-R, C-Met and HGF and PTEN (Mao et al, 2012).

Besides GBM, which features the highest grade of malignancy among glioma (grade IV), lower grade glioma which include grade II and grade III are a heterogeneous group of tumors in which specific molecular features are associated with divergent clinical outcome.

FGFR-TACC fusion

Recently Singh et al. (Singh et al, 2012) reported that a small subset of GBMs (3.1%) harbors oncogenic chromosomal translocations that fuse in-frame the tyrosine kinase coding domains of fibroblast growth factor receptor (FGFR) genes (FGFR1 or FGFR3) to the transforming acidic coiled-coil (TACC) coding domains of TACC1 or TACC3, respectively.

Lentivectors expressing FGFR-TACC fusions injected directly into short term astrocytic cell cultures as well as the brain parenchyma of mice have been shown to fully recapitulate GBM. Subsequently FGFR-TACC induced GBM (and derived cell lines) were successfully treated with FGFR inhibitors such as BGJ398, abolishing the malignant phenotype. Subsequently FGFR3-TACC3 fusions have been identified in pediatric and adult gliomas (Zhang et al, 2013). Recent data shows that FGFR amplification is a poor surrogate for fusion presence and that patients identified with FGFR-TACC fusions in GBM and other gliomas shows radiological evidence of response when treated with FGFR inhibitors (Di Stefano et al, 2015).In conclusion, FGFR-TACC fusions could potentially identify a subset of patients with GBM and/or other glioma subtypes who would benefit from targeted FGFR kinase inhibition.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of BGJ398

BGJ398 is an orally bio-available, selective and ATP competitive pan-fibroblast growth factor receptor (FGFR) kinase inhibitor which has demonstrated anti-tumor activity in preclinical, *in vitro* and *in-vivo* tumor models harboring FGFR genetic alterations. BGJ398 belongs to the pyrimidinyl aryl urea chemical class and its chemical name is 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-{6-[4-(4-ethyl-1-piperazin-1-yl)phenylamino]-pyrimidinyl-4-yl}-1-methylurea phosphate(1:1).

Please refer to the [Investigator's Brochure] for additional information on BGJ398.

1.2.1.1 Non-clinical experience

At the cellular level, BGJ398 selectively inhibits the kinase activity of FGFR1 FGFR2, FGFR3, and FGFR4 as measured by inhibition of receptor autophosphorylation with IC50 values of 3 - 7 nM for FGFR1, FGFR2 and FGFR3, and 168 nM for FGFR4. In cellular kinase selectivity assays using a panel of BaF3 cell lines rendered IL-3 independent by various tyrosine kinases, the most potently inhibited kinase, in addition to the FGFRs were VEGFR2 and FLT1 with IC50s of 1510 nM and 1591 nM, respectively.

Consistent with inhibition of FGFR autophosphorylation, BGJ398 inhibits FGFR downstream signaling and proliferation of human cancer cell lines harboring genetic alterations of the FGFRs. These include, among others, lung and breast cancer cell lines with FGFR1 gene amplification, gastric cancer with FGFR2 gene amplification, endometrial cancer with FGFR2 mutations and bladder cancer with FGFR3 mutations or FGFR3 translocations (Wesche et al, 2011). In line with its cellular activity, BGJ398 shows anti-tumor activity in multiple models bearing FGFR genetic alterations (Guagnano et al, 2012; Konecny et al, 2013).

1.2.1.1.1 Animal drug metabolism and pharmacokinetics

In all species tested, BGJ398 exhibited a high plasma CL and a large Vss. The compound is highly bound to plasma proteins (~ 98%) but does not preferentially distribute to red blood cells. BGJ398 is widely distributed to tissues in the rat and has a high affinity to melanin containing tissues. *In vitro* hepatic systems metabolize BGJ398 predominantly to 2 pharmacologically active metabolites: BHS697 and BQR917. Biotransformation of BGJ398 to both metabolites

was observed in human hepatocyte cultures. The compound is a P-gp and BCRP substrate and also inhibits BCRP mediated transport with an IC_{50} value of 0.21µM. BGJ398 is a potent reversible inhibitor of CYP3A4 (Ki 0.26µM). The compound also reversibly inhibits CYP2C9 and CYP2C19 with Ki of 6.09µM and 4.1µM, respectively and CYP2C8 with IC_{50} of 12µM. BGJ398 is also a time dependent inhibitor of CYP3A4 with a K_I = 37.3 µM and Kinact = 0.0547 min^{-1}. In addition CQM157, a recently identified metabolite in circulating plasma from patients, is an inhibitor of CYP2C8, CYP2C9 and CYP3A4 (IC_{50} less than 10 µM) and CYP2C19 (IC_{50} 12 µM). CQM157 is also an inhibitor of transporters P-gp, BCRP, OATP1B1 and OATP1B3 (IC50 less than 5 µM).

A distribution study following single dose administration of [^{14}C]BGJ398 in rats showed evidence that radiolabeled components (BGJ398 and /or its metabolites) cross the blood brain barrier. Concentrations of BGJ398 and its active metabolite BHS697 were also detected in rat brain following a single oral administration of 10 mg/kg of BGJ398.

1.2.1.1.2 Safety pharmacology and toxicology

BGJ398 showed no evidence of *in vitro* genotoxicity in Ames and chromosome aberration tests and no evidence of phototoxicity in a 3T3 photo-cytotoxicity test. *In vitro* safety pharmacology assessment of BGJ398 revealed a decrease in human *Ether-à-go-go*-related gene (hERG) channel activity with an IC_{50} of 2.0 µM (1121ng/ml).

In vivo safety pharmacology studies in rats and dogs did not reveal any effects on central nervous or respiratory systems and on hemodynamic or electrocardiographic parameters, respectively.

In repeated dose (oral gavage; up to 4-weeks) toxicity studies, BGJ398 did lead to increases in serum FGF23 and serum phosphorous associated with partially reversible ectopic mineralization (kidney, lung, vascular and digestive systems) along with largely reversible changes in renal function parameters and bone growth plate thickening / retention of the primary spongiosa in rats (≥ 10 mg/kg/day) and dogs (≥ 10 mg/kg/day). These effects were deemed to be on-target effects mediated by pharmacological inhibition of FGFR.

In rats, corneal changes were found upon 4 weeks of BGJ398 treatment consisting of irreversible, slight corneal opacity in dose-dependent incidence, as assessed by *in vivo* ophthalmology, associated with reversible, diffuse epithelial keratopathy at the highest dose of 10 mg/kg. In the 4-week GLP oral toxicity study in rats, the severely toxic dose in 10% (STD_{10}) was 10 mg/kg/day which resulted in premature death in one (1/30) animal. Doses of 20 mg/kg/day in rats led to vasculopathy associated with moribundity after 6 administrations. In dogs, the highest non-severely toxic dose (HNSTD) was 10 mg/kg/day leading to minimal, fully reversible retention of the primary spongiosa and minimal increase in mineralization in lung and kidney without observed functional impairment.

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety

As of November 6, 2014, 226 patients have received BGJ398 on one of the eight clinical trials. In addition to this phase II trial, BGJ398 is being evaluated in three phase I trials, one other monotherapy phase II study, two healthy volunteer studies and an individual patient protocol

(protocol to patient trial) that provides BGJ398 treatment to patients with tumors with FGFR genetic alterations who are not covered by available trials or are unable to travel to study centers. The dose escalation portion of the first in human phase I study (CBGJ398X2101) has been completed and the MTD has been identified as 125 mg once daily (q.d.), administered continuously. BGJ398 was evaluated at 9 different dose levels, ranging from 5 mg per day to 150 mg per day. The adverse events suspected to be related to BGJ398 that occurred in more than 20% or more patients who received BGJ398 were hyperphosphatemia (71.3%), decreased appetite (26.6%), fatigue (25.5%), stomatitis (24.5%), and alopecia (21.3%). Twenty-seven percent of patients (26/94) experienced at least one grade 3 or 4 event. Overall, most adverse events reported have been mild to moderate in severity and unrelated to BGJ398. Please refer to Investigator Brochure for more information.

Four dose limiting toxicities (DLTs) were reported during the dose escalation portion and occurred at the 100 mg (n=1; grade 3 AST/ALT elevation), 125 mg (n=1; hyperphosphataemia for > 14 days), and 150 mg (n=2; grade 1 corneal toxicity and grade 3 AST/ALT elevation) dose levels.

Enrollment is continuing in the dose expansion phase of the study at the 125 mg dose level in three out of four arms. One arm, which enrolled patients with any solid tumor type with FGFR genetic pathway alterations on a continuous schedule, has been closed due to completing enrollment. Of the three open arms, one arm is enrolling patients with FGFR1-amplified squamous non-small cell lung cancer, with dosing on a continuous 28 day cycle. A second arm is enrolling patients with advanced solid malignancies with any FGFR alteration and a third arm is enrolling patients with advanced or metastatic urothelial cell carcinoma with FGFR mutation or gene fusion. Patients enrolled to these latter two arms receive BGJ398 at 125 mg q.d. on a 3 weeks on/1 week off drug schedule, repeated in 28 day cycles.

The treatment emergent adverse events that occurred in 20% or more patients that were reported as of October 1, 2014 were increases in blood phosphorus [which include AE term of hyperphospatemia] (74%), constipation (40.8%), decreased appetite (40.8%), diarrhea (36.7%), stomatitis (36.7%), nausea (32.5%), fatigue (31.7%), alopecia (25.8%), asthenia (20.0%), blood creatinine increased (20.0%), and dry mouth (20.0%). The majority of the adverse events were Grade 1 and 2 and were reversible upon discontinuation of study drug. Additional information about the nature of these AEs and the dose levels at which they occurred can be found in the most recent version of the BGJ398 Investigator Brochure.Hyperphosphatemia has been seen in the majority of patients treated at doses of 100 mg q.d. and higher. Phosphate elevations are a biomarker of on-target FGFR pathway inhibition which mediates renal tubular phosphate secretion and reabsorption. Inhibition of this pathway leads to inability to secrete phosphate and secondary elevations in FGF23. The hyperphosphatemia has been managed in Phase I study by dietary phosphate restrictions, phosphate lowering therapy, drug interruptions, and dose reductions, which led to the introduction of the alternate 3 weeks on/1 week off drug schedule. Preliminary safety data with this schedule suggests improved tolerability and compliance with drug administration (e.g. fewer dose interruptions during cycle 1), though dose reductions in later cycles of therapy are not uncommon. As of March 15, 2014 data cut off, 17 out of 25 patients (68%) who received BGJ398 on the 3 week on/1 week of schedule experienced elevated phosphorus and only 4 patients (16%) required cycle 1 interruptions or reductions. In contrast, 41 out of 47 patients (87%) on the continuous dosing cycle experienced serum phosphorus

elevations. Twenty patients (43%) required cycle 1 dose interruptions and 13 patients (28%) required dose reductions during cycle 1. Please refer to the BGJ398 Investigator Brochure for additional information.

1.2.1.2.2 Preliminary efficacy of BGJ398

Preliminary anti-tumor activity, including durable partial responses (PRs), was noted in the phase I first-in-human trial (BGJ398X2101) in patients treated at doses of >100mg of BGJ398 with the following tumor types: FGFR1 amplified squamous NSCLC, FGFR amplified squamous cell carcinoma of the head and neck, FGFR1 amplified breast cancer, FGFR3 mutated bladder cancer, and advanced cholangiocarcinoma with FGFR2 gene fusion.

1.2.1.2.3 Clinical pharmacokinetics

In Study BGJ398X2101, full PK profiles were obtained on Day 1, Day 15 and Day 28 after the first dose of study drug. As this study is ongoing, all data presented are current as of 02 September 2012 (refer to the Investigator Brochure for further details).

At 5 and 10 mg/day, plasma concentrations of BGJ398 were low (< 3.3 ng/mL) and frequently below the lower limit of quantification. Exposure (Cmax and AUC) was measurable in all treated patients starting at 20 mg/day.

The median apparent Tmax value across all dose levels tended to be 2-3 hours post-dose. At the MTD (125 mg q.d.), the Cmax and AUC0-24 were ~111 ng/ml and ~817 h.ng/ml on Day 1 and ~318 ng/mL and ~5301 h.ng/mL on Day 15.

The inter-patient variability was moderate to high for BGJ398 and % coefficient of variation (% CV) ranged from 30 – 110 % for dose groups 20-150 mg on Day 15. The exposure differed significantly between some patients at the same dose levels. At the MTD dose of 125 mg, high inter-individual variability was observed on Day 1 (101% and 94% CV for Cmax and AUC0-24, respectively). This inter-individual variability appeared to decrease on Day 15 (35% and 41 % in CV% for Cmax and AUC0-24).

Accumulation was observed with daily dosing. The mean AUC0-24 ratios between Cycle 1 Day 1 and Cycle 1 Day 15 ranged from 1.5 to 6.5, which indicates some change in BGJ398 exposure following multiple dosing. At doses of 60 mg and above, most individual patients showed increased exposure on Day 15 following multiple dosing (~1.5 – 13 fold relative to Day 1 exposure). Very limited data are available for patients who received continuous dosing for 28 days without dose interruptions (8 patients at doses 60 mg and above, only 7 patients with PK data). In most of these patients who received uninterrupted dosing, a further increase in exposure beyond Day 15 was observed. This is based on either AUC0-24 exposure on Day 28 or comparing predose samples after Day 15 in these patients. Refer to the BGJ398 Investigator's Brochure for further details.

In most patients, across all study days and dose levels, active metabolites were measurable. As a percentage of parent exposure, BHS697 was detected at ~10-15% and BQR917 at < 10%.

Following an exploratory analysis, CQM157 was identified as a major pharmacologically active metabolite in plasma samples with in vitro potency that was similar to BGJ398. Preliminary analysis in circulating plasma following dosing with 125 mg of BGJ398 on Day 1 (n=9), showed

plasma exposures to CQM157 were as high as parent BGJ398 (up to ~3X). On Day 15 (n=5), exposure to CQM157 remained the same or decreased as compared to Day1 unlike BGJ398 which showed accumulation following multiple dosing.

2 Rationale

2.1 Study rationale and purpose

GBM is characterized by heterogeneous and complex genetic alterations. Common alterations found in GBM include: EGFR overexpression (70%) (Maher et al, 2006); TP53, RB, INK4a, PDGF-R, VEGF-R, C-Met and HGF and PTEN (Mao et al, 2012). The activity of many of the more common oncogenes have been noted to be upregulated (either through activating mutations or through over-expression) and the activity of many of the more common tumor suppressor genes have been noted to be down-regulated (either through inactivating mutations or deletion). As often seen with genomically complex disease, there are limited effective clinical options and combination therapies have been the standard clinical trial approach (Mao et al, 2012)

Recently Singh et al (Singh et al, 2012) using whole-transcriptome sequencing identified novel FGFR-TACC fusions in short term cultures isolated from nine patients with primary GBMs. Based on the identification of these novel fusions models expressing FGFR-TACC within astrocytes both in vitro and in vivo were generated and recapitulated GBM-like malignancies. Finally they demonstrated that FGFR inhibition reverses the malignant phenotype. Specifically, BGJ398 was used in several *in vitro* experiments as part of this work showing growth inhibition of FGFR-TACC based GBM models. The reversal of the established GBM phenotype by FGFR inhibitors BJG398 and AZD4547 clearly establishes a role for FGFR inhibition in the treatment of GBMs characterized by FGFR-TACC fusions. Furthermore, this work clearly suggests that patients with GBM characterized by FGFR-TACC fusions may be successfully treated solely (i.e., as a single agent) with a therapeutically active FGFR inhibitor. More recently JNJ-42756493, a potent, oral pan-FGFR tyrosine kinase inhibitor with IC50 values in the low nanomolar range for all members of the FGFR family has shown evidence of radiological response in GBM patients harboring FGFR-TACC fusions [Di Stefano et al 2015].

Additionally the presence of the fusion is mutually exclusive of EGFR, PDGFR, or MET amplification (Parker et al 2013) in GBMs further suggesting the oncogenic dependency of the FGFR-TACC fusion on those GBMs.

These preclinical findings support the initiation of a clinical trial to assess the efficacy of BGJ398 in the treatment of GBM in patients with evidence of FGFR translocation or mutation.

2.2 Rationale for the study design

This is a phase 2, multicenter, open-label study of BGJ398 in patients with recurrent resectable or unresectable GBM and/or other glioma subtypes with evidence of FGFR translocation or activating mutation. Patients will be enrolled in two groups. Combined data from both these groups will provide enough information for the primary analysis of this study in a reasonable time-frame. [redacted]

Group 1 will enroll recurrent, unresectable patients with GBM and/or other glioma subtypes with evidence of FGFR translocation or activating mutations who will receive BGJ398 125mg p.o. daily three weeks on / one week off (days 1-21 of every 28).

Group 2 (surgical) will enroll recurrent, resectable patients with GBM and/or other glioma subtypes with evidence of FGFR translocation or activating mutation who will receive BGJ398 125 mg p.o. daily presurgically for 5-10 days (a 5-day range will be allowed to accommodate surgical delays due to logistical issues). [redacted] Patients will resume treatment and receive BGJ398 125mg p.o. daily three weeks on / one week off (as in group 1), at a minimum of 2 weeks and no more than 6 weeks following surgery, unless agreed otherwise between Novartis and the investigator.

2.3 Rationale for dose and regimen selection

The rationale for treatment dose and schedule is based on the clinical data available to date from the first in human dose escalation study.

The dose escalation portion of the study has been completed and the MTD has been identified as 125 mg once daily (q.d.), administered continuously. Results showed drug concentrations within the predicted efficacious dose range and signs of clinical activity (tumor size reduction by CT scan). However, most of the patients treated at these efficacious doses experienced reversible toxicities (mainly hyperphosphatemia) leading to study drug interruption. Based on the drug administration record, the median time until first dose interruption was approximately 23 days for patients treated at 100mg and 22 days for patients treated at 125mg. Drug was discontinued for a median time of 7 days. A “three week on, one week off” schedule of 125mg p.o. is currently being explored as part of the ongoing CBJ398X2101. As of 01 May 2013, 7 patients have been enrolled on this schedule and two have completed one cycle without dose interruption.

The current study will employ the “3 week on, one week off” schedule with BGJ398 dosed at 125mg p.o. q.d. Phosphate binders will be used prophylactically.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

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

The primary endpoint will be the progression-free survival rate at 6 month (PFS6 rate) based on patients pooled from Group 1 and Group 2. Numerous clinical trials in recurrent GBM have confirmed the equivalency of the 6 month PFS rate in the resected and unresectable settings (Prados et al, 2011; Clarke et al, 2011; Lamborn et al, 2008).

The secondary objectives of the study are to assess the anti-tumor activity for patients with recurrent GBM and/or other glioma subtypes that harbor FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, 2or 3 based on ORR and OS and to characterize the safety and tolerability of BGJ398.

The secondary efficacy endpoints will be the objective response rate of patients from Group 1 and Group 2 with radiologically assessable enhancing disease using RANO criteria and OS.

The secondary safety and tolerability endpoints are listed in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
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 (Appendix 3) as assessed by the investigator	
Secondary		Refer to Section 10.5
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 (Appendix 3) as assessed by the investigator	
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	

[redacted]

4 Study design

4.1 Description of study design

This is a multi-center, open label, phase II study, with 2 groups of patients. BGJ398 will be administered once daily as an oral single agent in 28-day cycles, on a "3 weeks on, one week off schedule." The study will enroll patients with recurrent GBM and/or other glioma subtypes, whose tumors harbor FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, FGFR2or FGFR3 gene.

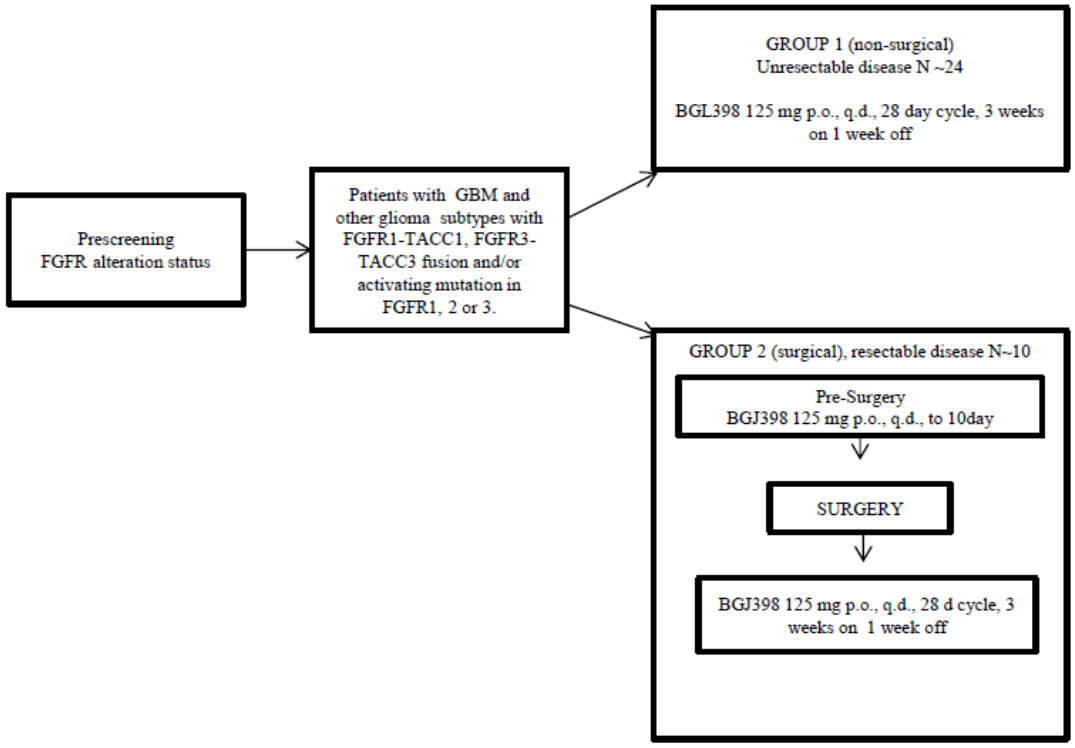
Group 1 will target patients with RANO tumor progression not eligible for surgical resection. As the primary endpoint is the 6 month progression-free survival rate. Additionally, patients who recently underwent resection and are post-operative without RANO tumor progression may also be eligible for group 1 assuming all inclusion/exclusion criteria are met and most recent surgery has occurred within six weeks of planned first treatment dose.

Group 2 will target patients who will have cytoreductive surgery for recurrent disease as part of their routine care. Patients enrolled to group 2 will receive BGJ398 for 5 to 10 days prior to resection. [redacted] Following recovery from surgery (a minimum of 2 weeks and no more than six weeks post operatively unless agreed otherwise between Novartis and the Investigator, on a case by case basis), these patients will receive BGJ398 in 28-day cycles, as for patients in group 1. If a patient assigned to group 2 does not undergo planned surgical resection, then the patient will be allowed to continue therapy as per group 1. If a patient enrolled to group 2 needs to undergo surgical resection sooner than initially planned (and having had less than 5 days of BGJ398), then the patient will still be allowed to continue therapy post-surgically as per group 2 regardless of the number of days the patient received BGJ398 pre-surgically.

A total of 34 patients will be enrolled, and it is expected that the ratio of patients in group 1 and group 2 will be approximately 2:1, based on previous GBM trials (Stupp et al 2006, Wong et al 1999; Lamborn et al 2008; Wong et al 2011; Hofer et al 2011; Wen et al 2009; Norden et al 2008; Yung et al 2000). Please see Section 10: Statistical Methods and Data for details.

In order to assess the antitumor activity of BGJ398, patients will be evaluated for tumor response and progression by Gd-enhanced MRI every 8 weeks until disease progression or discontinuation from study using RANO criteria.

Figure 4-1 Study design



Molecular pre-screening

Evidence of FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, FGFR2, or FGFR3 is required in order to begin study screening. [redacted]

[redacted]

- If pre-screening data is not available at the time of study entry, the patient must sign the molecular pre-screening consent to allow for the collection and/or submission of samples to the Novartis designated laboratory for analysis.

If the local data or the results of the central analysis meet inclusion criteria (Section 5.2), the patient can proceed with the screening procedures.

Patients identified to have an activating mutation in FGFR1, 2 or 3 may be eligible pending agreement between Novartis and Investigator.

Screening

The screening period begins once the patient has signed the study informed consent. All screening evaluations are required to be performed before study treatment administration begins. Evaluations that were conducted prior to the signing of the informed consent document as a part of standard of care analysis may be used to demonstrate eligibility as long as the evaluations were conducted within allowed screening windows.

Treatment period

For patients in group 1 (non surgical group, unresectable disease), the treatment period will begin on cycle 1, day 1 and will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, or death.

For patients in group 2 (surgical group, resectable disease), the treatment will begin 5-10 days prior to surgery with the last pre-surgical dose given within 24 hours of surgery. The duration of the treatment before surgery (5 to 10 days) will be left at the investigator discretion. Patients will be expected to resume the treatment upon surgical recovery (a minimum of 2 weeks and no more than 6 weeks post operatively, unless agreed otherwise between Novartis and the Investigator, on a case by case basis). The post surgical treatment will begin as cycle 1, day 1 and will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, or death.

End of treatment

The EOT visit occurs within 14 days after last administration of study treatment (Section 7.1.4). All participating patients must complete this visit even if they have had to discontinue prematurely unless they are unable or unwilling to return.

Follow up

All patients will be followed up as described in Section 7.1.5.

30-day safety follow-up period

All patients must be followed up for safety assessments during 30 days after the last dose of the study treatment.

Disease progression follow-up period

All patients enrolled in the study who discontinue study treatment for any reason other than disease progression will be followed up monthly via a phone call and will have MRI scan every 8 weeks, until disease progression or the initiation of subsequent anticancer therapies, or death, whichever occurs first.

Survival follow-up period

All patients enrolled in the study will be followed e.g., phone call for survival every 4 months for at least one year per e.g., phone call per, after last patient last treatment (LPLT).

4.2 Timing of interim analyses and design adaptations

An interim analysis will be carried out once 10 patients in total for both groups have completed 6 cycles of treatment or discontinued earlier. Based on the interim analysis results, the decision to continue or not with the recruitment will be made (Section 10.7). Accrual will continue during the interim analysis.

4.3 Definition of end of the study

End of study will be upon completion of the follow up period for the last patient treated as described in Section 7.1.5. This will be either upon study completion of the last patient treated or once the last patient has expired or all patients have completed the study and have been followed for at least one year after their first dose of study treatment, have been lost to follow-up, or withdrew consent, whichever occurs first.

The analysis of study data will be based on all patients' data up to the time when all patients have potentially completed at least 6 cycles of treatment or discontinued the study. This will be the cut-off point for the primary clinical study report (CSR). The additional data for any patients continuing to receive BGJ398 beyond the cut-off point for the primary clinical study report (CSR), as allowed by the protocol, 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.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.4 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial, and of the early termination of the trial for a prematurely withdrawn patient.

5 Population

5.1 Patient population

Adult patients with histologically confirmed GBM and/or other glioma subtypes with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, 2 or 3. who have evidence of radiographic progression following either first line standard therapy or therapy for recurrent disease will be enrolled in this study.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. They can participate in observational studies. Patients who have completed the study may not be re-enrolled for a second course of treatment. Patients who do not meet all of the inclusion or exclusion criteria may be re-screened for consideration in the trial. If a patient is re-screened, the same subject ID number should be used.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patients with histologically confirmed GBM and/or other glioma subtypes at the time of diagnosis or prior relapse. Note that all subtypes of gliomas are permitted. Any question of eligibility should be discussed with Novartis.
2. At least 15-20 unstained slides and/or a tumor block from at least one prior surgery must be available for molecular testing, unless agreed otherwise between Novartis and the Investigator.
3. Written documentation of local or central laboratory determination of FGFR1-TACC1, FGFR3-TACC-3 fusion and/or activating mutation in FGFR1, FGFR2or FGFR3 is required. Patients identified to have an activating mutation in FGFR1, 2 or 3 may be eligible pending agreement between Novartis and Investigator
4. RANO defined tumor progression by MRI (or CT for patients who cannot tolerate MRI) in comparison to a prior scan; OR, progression that does not meet RANO criteria if the disease progression is otherwise obvious in the opinion of the investigator and is discussed with Novartis OR histologically proven recurrent/progressive disease based on histology if surgery was the treatment for the most recent progression.
5. Patients must have received prior external beam radiotherapy and temozolomide.
6. Unlimited prior surgeries and chemotherapies are permitted.
7. Group specific inclusion:
    a. Group 1: RANO defined tumor progression as per Inclusion Criteria 4. Additionally, patients who recently underwent resection for RANO defined contrast enhancing tumor progression and are post-operative without evidence of RANO tumor progression may also be eligible for group 1 assuming all inclusion/exclusion criteria are met and the most recent surgery has occurred within six weeks of the planned first treatment dose.
    b. Group 2: RANO defined tumor progression as per Inclusion Criteria 4 and planned surgical resection. If a patient assigned to group 2 does not undergo planned surgical resection, then the patient will be allowed to continue therapy as per group 1. If a patient enrolled to group 2 needs to undergo surgical resection sooner than initially planned (and having had less than 5 days of BGJ398), then the patient will still be allowed to continue therapy post-surgically as per group 2 regardless of the number of days the patient received BGJ398 pre-surgically.
8. Patients ≥18 years of age.

9. ECOG performance status ≤ 2. Assessment via Karnofsky Performance Status (KPS) and subsequent conversion to ECOG is acceptable (Ma et al, 2010).
10. Able to read and/or understand the details of the study and provide written evidence of informed consents as approved by IRB/EC.
11. Recovery from adverse events of previous systemic anti-cancer therapies to baseline or no more than grade 2, except for the following:
    a. Alopecia
12. Able to swallow oral medication.
13. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria prior to the first treatment.

1. History of another primary malignancy except: in situ carcinoma of any-type that has been adequately treated; or non-melanoma carcinoma of the skin; or any other curatively treated malignancy that has not been treated in the prior 3 months or expected to require treatment for recurrence during the course of the study; or any indolent malignancy that has not required treatment within the prior 2 years (even if never previously treated).
2. Prior or current treatment with a FGFR inhibitor (unless agreed otherwise between Novartis and the Investigator on a case by case basis).
3. Neurological symptoms related to underlying disease requiring increasing doses of corticosteroids. **Note***:* Steroid use for management of CNS tumors is allowed but must be at a stable dose for at least 1 week preceding the baseline MRI/CT. If the corticosteroid dose is increased between the date of imaging and the initiation of study treatment, a new baseline MRI/CT is required. Definition of stable steroids includes patients on no steroids. Local administration methods or prophylactic use is allowed.
4. Any other medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures.
5. History and/or current evidence of tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium and lung with the exception of calcified lymph nodes and asymptomatic coronary calcification.
6. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BGJ398 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
7. History and/or current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis, etc.
8. Treatment with any of the following anti-cancer therapies prior to the first dose of BGJ398 within the stated timeframes:
    - Cyclical cytotoxic chemotherapy within a period of time that is shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C)

- Biological therapy (e.g., antibodies – including bevacizumab) within a period of time that is ≤ 5 $t_{1/2}$ or ≤ 4 weeks, whichever is shorter, prior to starting study drug
- Continuous or intermittent small molecule therapeutics (excluding traditional cytotoxic chemotherapy) within a period of time that is ≤ 5 $t_{1/2}$ or ≤ 4 weeks (whichever is shorter) prior to starting study drug
- Any other investigational agents within a period of time that is ≤ 5 $t_{1/2}$ or less than the cycle length used for that treatment or ≤ 4 weeks (whichever is shortest) prior to starting study drug
- Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug

9. Patients who are currently receiving treatment with agents that are known strong inducers or inhibitors CYP3A4 are prohibited. (Refer to Appendix 2 for prohibited medications).
10. Patients taking Enzyme Inducing Anti-Epileptic Drug (EIAED). If previously on an EIAED, the patient must be off of it for at least two weeks prior to study treatment. (Refer to Appendix 2 for list of prohibited medications).
11. Consumption of grapefruit, grapefruit juice, pomegranates, star fruits, Seville oranges or products within 7 days prior to first dose.
12. Use of medications that are known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes 7 days prior to first dose.
13. Use of amiodarone within 90 days prior to first dose.
14. Use of medications that increase serum levels of phosphorus and/or calcium.
15. Current use of therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulants. Heparin and/or low molecular weight heparins are allowed.
16. Insufficient bone marrow function:
    - ANC <1,000/mm^3 [1.0 x 10^9/L]
    - Platelets < 75,000/mm^3 [75 x 10^9/L]
    - Hemoglobin < 9.0 g/dL
17. Insufficient hepatic and renal function:
    - Total bilirubin > 1.5x ULN unless bilirubin elevation is related to Gilbert's Syndrome for which bilirubin ≥ 2.5 ULN is an exclusion
    - AST/SGOT or ALT/SGPT > 2.5x ULN (AST or ALT > 5x ULN in the presence of liver metastases)
    - Serum creatinine > 1.5xULN and calculated or measured creatinine clearance < 45mL/min
18. Calcium-phosphate homeostasis:
    - Inorganic phosphorus outside of institutional/laboratory normal upper limits
    - Total serum calcium (can be corrected) outside of institutional/laboratory normal upper limits
19. Clinically significant cardiac disease including any of the following. Note that this applies only to patients who have a documented or suspected history of cardiac disease and cardiac testing is not otherwise required.

- Congestive heart failure requiring treatment (NYHA grade ≥ 2), LVEF < 50 as determined by MUGA scan or ECHO, or uncontrolled hypertension (refer to WHO-ISH guidelines)
- History or presence of clinically significant ventricular arrhythmias, atrial fibrillation, resting bradycardia, or conduction abnormality
- Unstable angina pectoris or acute myocardial infarction ≤ 3 months prior to starting study drug
- QTcF > 470 msec
- History of congenital long QT syndrome
- Clinically significant hypokalemia, which cannot be corrected

20. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
21. HIV positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with study drug. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. This applies only to patients who have a documented history of HIV and HIV testing is not otherwise required.
22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months following the discontinuation of study treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Combination of the following (a+b):
        a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
23. Current evidence of corneal/keratopathy or retinal disorder including, but not limited to, bullous/ band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivits, confirmed by ophthalmologic examination

Post-menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without

hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6 Treatment

The investigational drug will be BGJ398 as an oral formulation.

6.1 Study treatment

The pharmacist will dispense the correct number of capsules that will ensure that each patient receives sufficient drug until the next scheduled study visit.

Study drug labels will comply with the legal requirements of each country and be printed in the local language.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Strength	Frequency and/or Regimen
BGJ398	Capsule for oral use	100 mg	Daily, 3 weeks on 1 week off schedule
BGJ398	Capsule for oral use	25 mg	Daily, 3 weeks on 1 week off schedule

Patients should be instructed to take the daily dose of BGJ398 in the morning, at approximately the same time each day (24 ± 2 hrs. interval), [redacted] The investigator should instruct the patient to take the study drug exactly as prescribed to promote compliance. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.1.1.1 Instructions for administration of BGJ398

- Patients should consume a light breakfast each day (e.g., non-grapefruit-based juice, toast and jam), [redacted]. This should be followed by a 2 hour fast, after which the doses of study drug should be taken. Patients should continue to fast for 1 hour after the administration of study drug.
- BGJ398 should be taken with a large glass of water (~250 mL) and consumed over as short a time as possible. Patients should be instructed to swallow the capsules whole and not chew them.
- If for any reason a breakfast was not consumed prior to taking the dose the patient should take the dose with a full glass of water, and continue to fast for an hour after taking the dose.
- If the patient forgets to take the scheduled dose in the morning, he/she should not take the dose more than 2 hours after the usual time and should continue treatment the next day. Any doses that are missed should be skipped altogether and should not be replaced or made up at the next scheduled dosing.
- If vomiting occurs following the dosing of study drug, re-dosing is not permitted that same day. Dosing should resume the next day. [redacted]
- BGJ398 is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of both compounds, and limit bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Therefore, BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.
- Patients must avoid consuming Seville oranges or juice, grapefruit, grapefruit juice, grapefruit hybrids, star fruits, pomegranates, or pummelos from 7 days prior to the first dose of study medication through the end of study participation. This is due to a potential CYP3A4 interaction with study medication. Normal oranges and orange juice are allowed.
- The investigator or responsible site personnel should instruct the patient to take the study drug exactly as prescribed to promote compliance. All dosages prescribed and dispensed to the patient and all dose changes or missed doses during the study must be recorded on the Dosage Administration Record eCRF.
- Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drug to the site at the end of each cycle.

6.1.2 Ancillary treatments

Phosphate-lowering therapy may be initiated as clinically indicated.

Phosphate lowering treatment, including but not restricted to low phosphate diet and phosphate binding therapy such as sevelamer hydrochloride, should be implemented and modified as clinically indicated, including prophylactically, at study drug initiation and throughout BGJ398 administration. Recommendations for treatment are provided in Section 6.2.2 (Follow up on drug induced toxicities), but should be modified as per country or institutional guidelines.

6.1.3 Supportive treatment needed for GBM

During the course of this trial, the use of systemic anti-coagulation (such as with heparinoids or direct thrombin inhibitors) in the setting of venous thromboembolism (VTE) will be performed according to the judgment of the investigator. Prophylactic anti-coagulation with heparin or low molecular weight heparin (LMWH) is allowed.

6.1.4 Treatment duration

Patients in the surgical group will be treated with BGJ398 once daily for 5 to 10 days before surgery.

Patients from both groups being treated with BGJ398 on a three week on, one week off schedule may continue treatment with BGJ398 until patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent or if the study is terminated prematurely by Novartis.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. These changes must be recorded on the Dosage Administration Record CRF.

All dose modifications should be based on the worst preceding toxicity. The following guidelines need to be applied:

Each patient will be allowed up to 2 dose reductions. Patients must discontinue BGJ398 if toxicities persist following 2 dose reductions (Table 6-2) unless a continuation is allowed in discussion with Novartis.

Following resolution of toxicity to baseline or ≤ grade 1, treatment is resumed at either the same or lower doses of study drugs as per the criteria in Table 6-3. If treatment is resumed at the same doses of study drugs, and the same toxicity recurs with the same or worse severity regardless of duration, doses must be reduced to the next lower dose level (Table 6-2). If treatment is resumed at the lower doses of study drugs, and the same toxicity recurs with the same or worse severity, the patient must discontinue study treatment unless a continuation is allowed in discussion with Novartis.

If a patient requires a dose delay of > 14 consecutive days of BGJ398 from the intended day of the next scheduled dose, then the patient should be discontinued from the study treatment unless a continuation is allowed in discussion with Novartis.

Patients who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed as described in Table 6-3 and Section 6.2.2.

In exceptional situations, study treatment may continue even if the patient experienced one of the treatment stopping rules. The decision to allow for continuation of treatment will be made on a case-by-case basis following discussion between Novartis and the Investigator.

Situations that may allow for continuation of treatment include but are not limited to the following.

- A dose delay of > 14 days has occurred, but the patient is clearly benefiting from study treatment (i.e., stable disease, partial response, or complete response) and it is the investigator's opinion that no safety concerns are present, after discussion with Novartis Medical Monitor, the patient may remain on the study treatment
- A third or subsequent reduction (to 50 mg) in dose may be allowed if the patient is clearly benefiting from study treatment (i.e., stable disease, partial response, or complete response) but is experiencing adverse events that prevent continued treatment at the already reduced dose.

Table 6-2 Dose reduction table

Dose level	BGJ398	
Dose level 0	125 mg	Starting dose
Dose level -1	100 mg	
Dose level -2	75 mg	
Dose level -3	50 mg	Allowed only if patients is clearly benefiting from study treatment, but is experiencing AE that prevent continued treatment at dose level -2

Table 6-3 Criteria for interruption and re-initiation of BGJ398 treatment

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Cardiac disorders	
Cardiac - Prolonged QTcF interval	
Grade 1 and 2 : QTcF ≥ 481msec and ≤ 500 msec (asymptomatic)	Maintain dose level of BGJ398 ● ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1, or as clinically indicated If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. ● If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 for all subsequent cycles.
Grade 3 : QTcF > 500msec as identified on the ECG by the investigator	● Hold BGJ398. ● Monitor patient with hourly ECGs until the QTcF has returned to baseline. ● Perform further monitoring as clinically indicated. ● Exclude other causes of QTcF prolongation such as hypokalemia, hypomagnesaemia and decreased blood oxygenation. ● Patients should receive appropriate electrolyte replacement and should not receive further BGJ398 until electrolytes are documented to be within normal limits. Once the QTcF prolongation has resolved, patients may be re-treated at one lower dose level at the investigator's discretion ● ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1 or as clinically indicated ● If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. ● If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 or as clinically indicated, for all subsequent cycles ● Patients who experience recurrent QTcF ≥ 500msec after one dose reduction will be discontinued from study. NB: If ventricular arrhythmia or Torsades de Pointes is observed in a patient, he/she will be discontinued from the study. [redacted]

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Cardiac disorders - others Grade ≥ 3, or congestive heart failure ≥ 2	Discontinue patient from study treatment.
Investigations-Hematology	
ANC decreased (Neutropenia) Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1or baseline, then ● If resolved in ≤ 7 days, maintain dose level of BGJ398 ● If resolved in > 7 days, ↓ 1 dose level of BGJ398. Hold dose of BGJ398 until resolved to CTCAE ≤ Grade 1, ↓ 1 dose level of BGJ398.
Febrile neutropenia Grade 3 (ANC < 1.0 x 10^9/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C for more than one hour) Grade 4	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ● If resolved by ≤ 7 days, ↓ 1 dose level of BGJ398. ● If not resolved within 7 days discontinue patient from study drug treatment. Discontinue patient from study treatment.
Hemoglobin Grade 3 (<8.0 mg/dL – 6.5 mg/dL) Grade 4 (< 6.5 mg/dL)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline, then maintain dose level Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level
Platelet count decreased (Thrombocytopenia) Grade 3 (PLT < 50 - 25 x 10^9/L) without bleeding Grade 3 (PLT < 50 - 25 x 10^9/L) with bleeding or Grade 4 (PLT < 25 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline ● If resolved in ≤ 7 days, maintain dose level of BGJ398. ● If resolved in > 7 days, ↓ 1 dose level of BGJ398 Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Investigations – Renal	
Serum creatinine Grade 2 (> 1.5 - 3.0 x ULN) Grade ≥ 3 (> 3.0 x ULN)	If serum creatinine CTCAE Grade ≥ 2 has been demonstrated in conjunction with hyperphosphatemia, serum creatinine levels must be repeated at least weekly until resolution. 24-hour urine collection should be obtained as clinically indicated for total phosphate, calcium, protein, and creatinine clearance. Ultrasound examination of the kidneys should be performed as indicated to evaluate de-novo calcifications until resolution or stabilization of creatinine. Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline ● If resolved in ≤ 7 days, maintain dose level of BGJ398. ● If resolved in > 7 days, ↓ 1 dose level of BGJ398. Discontinue patient from study treatment
Investigations – Hepatic	
Blood bilirubin (patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only) Grade 2 (>1.5 – 3.0 x ULN) Grade ≥ 3 (> 3.0 x ULN)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 ● If resolved in ≤ 7 days, maintain dose level of BGJ398. ● If resolved in > 7 days, ↓ 1 dose level of BGJ398. Discontinue patient from study treatment. Note: If CTCAE Grade 3 or 4 hyperbilirubinemia is due to hemolysis, then ↓ 1 dose level of BGJ398 and continue treatment at the discretion of the Investigator.
AST or ALT Grade 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation > 2.0 x ULN	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline ● If resolved in ≤ 7 days, maintain dose level of BGJ398. ● If resolved in > 7 days, ↓ 1 dose level of BGJ398.

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Grade 4 (> 20.0 x ULN) without bilirubin elevation >2.0 x ULN	Discontinue patient from study treatment.
AST or ALT and Bilirubin AST or ALT > 3.0 – 5.0 x ULN and total bilirubin > 2.0 x ULN without liver metastasis or evidence of disease progression in the liver	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 ● If resolved in ≤ 7 days, ↓ 1 dose level of BGJ398. ● If resolved in > 7 days, discontinue patient from study treatment.
AST or ALT > 5.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue patient from study treatment.
Laboratory / Metabolic disorders	
Asymptomatic amylase and/or lipase elevation Grade 3 (> 2.0 - 5.0 x ULN) Grade 4 (>5.0 x ULN)	● Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 2. ● ↓ 1 dose level of BGJ398 For recurrent Grade 3 asymptomatic lipase or amylase elevation despite dose reduction, BGJ398 should be held and continuation of therapy should be discussed with the Novartis medical monitor following resolution to ≤ Grade 2 For any Grade 4 asymptomatic lipase or amylase elevation, BGJ398 should be held and continuation of therapy should be discussed with the Novartis medical monitor following resolution to ≤ Grade 2. Note*:* A CT scan or other imaging study to assess the pancreas, liver, and gallbladder should be performed as clinically indicated within 1 week of the first occurrence of any CTCAE ≥ Grade 3 amylase and/or lipase.
Grade 4 (> 5.0 x ULN)	Discontinue patient from study treatment
Hyperphosphatemia Serum phosphorus >5.5 – 7.0 mg/dL Serum phosphorus > 7.0 mg/dL for more than 7 days despite maximal phosphate lowering therapy (Sevelamer) **or** single serum phosphorus >	Maintain dose level of BGJ398 and optimize phosphate lowering therapy as clinically indicated. Hold BGJ398 dose until resolved to serum phosphorus ≤ 5.5 mg/dL.

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
9.0 mg/dL regardless of duration or dose of phosphate lowering therapy (Sevelamer). (Optimize/maximize dose and schedule of phosphate lowering therapy in accordance with package insert, country or institutional guidelines).	Restart BGJ398 at the same dose level with maximal phosphate binder dosing if the patient did not receive maximal phosphate binder dosing for serum phosphorus > 7.0 mg/dL for > 7 days. Reduce one dose level of BGJ398 if the patient had received maximal phosphate lowering therapy for serum phosphorus >7.0 mg/dL for > 7 days **or** if patient had a one-time serum phosphorus of > 9.0 mg/dL. Restart BGJ398 with maximal phosphate binder dosing. It is recommended that phosphate binder dosing continues during BGJ398 dose interruptions for hyperphosphatemia and that serum phosphorus values be monitored frequently, e.g. every 2-3 days. Phosphate binder dosing should be held during the week off BGJ398 therapy each cycle (Days 22-28) and during BGJ398 dose interruptions for non-hyperphosphatemia adverse events.
Hypercalcemia Serum calcium grade 2 Serum calcium ≥ grade 3	Hold BGJ398 dose until resolved to grade 1 or baseline: ● if resolved ≤ 7 days after suspending BGJ398, maintain dose level ● if resolved > 7 days after suspending BGJ398, ↓ 1 dose level Discontinue patient from the study
Nervous system disorders	
Neurotoxicity Grade 2 Grade ≥ 3	Omit dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398 Discontinue patient from study drug treatment
GI disorders	
Pancreatitis Grade ≥ 2	Discontinue patient from study drug treatment

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Diarrhea	
Grade 1	Maintain dose level of BGJ398, but initiate anti-diarrheal treatment
Grade 2	● Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 ● Optimize anti-diarrheal treatment, maintain dose level of BGJ398. ● For reoccurrence of diarrhea CTCAE Grade 2, hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, ↓ BGJ398 by 1 dose level
Grade 3	● Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 ● Optimize anti-diarrheal treatment ● ↓ BGJ398 by 1 dose level ● For reoccurrence of diarrhea CTCAE Grade 3, despite optimal anti-diarrheal treatment, discontinue patient from study treatment.
Grade 4	Discontinue patient from study treatment. Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea
Vomiting Grade 2 not controlled by optimal anti-emetic therapy	Hold BGJ398 doses until ≤ grade 1, ↓ 1 dose level
Grade 3 not controlled by optimal anti-emetic therapy or Grade 4	Discontinue patient from study

Worst Toxicity CTCAE using the current active CTCAE version	**Recommended Dose Modifications any time during a cycle of therapy**
Eye Disorders (confirmed by ophthalmologic examination)	
Retinal disorders Grade 2 CSR and CSR-like events	Hold BGJ398 until resolved to ≤ grade 1 and continue ophthalmologic evaluation ● If resolved in ≤ 14 days, ↓ BGJ398 by 1 dose level ● If resolved in > 14 days, discontinue BGJ398
Grade 3 CSR and CSR-like events and any other grade 3 eye disorders	Hold BGJ398 until resolved to grade ≤ 1. ● If resolved in ≤ 14 days, ↓ BGJ398 by 1 dose level ● If resolved in > 14 days, discontinue BGJ398
≥ grade 1 retinal vein occlusion, grade 4 CSR and CSR-like events, and grade 4 other eye disorders	Discontinue BGJ398
Other ocular/visual toxicity ≥ grade 3	Hold BGJ398 until resolution to ≤ grade 1 If resolution in ≤14 days, ↓ 1 dose level, otherwise discontinue BGJ398
General disorders	
Fatigue Grade 3	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 ● If resolved in ≤ 7 days, maintain dose level of BGJ398. ● If resolved in > 7 days, discontinue patient from study treatment.
Other clinically significant AEs	
Grade 3	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398.
Grade 4	Discontinue patient from study treatment.
All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it will not be increased at a later time even if there is no toxicity. Patients who require more than two dose reductions of BGJ398 will be discontinued from study drug treatment. If a patient requires a dose delay of > 14 days from the intended day of the next scheduled dose of BGJ398 then study treatment must be stopped.	

6.2.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. Clinical experts or specialists, such as ophthalmologist, endocrinologist, dermatologist, should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of BGJ398.

6.2.3 Anticipated risks and safety concerns of the study drug

Eligibility criteria as well as specific dose modification and stopping rules are included in this protocol. Guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., hyperphosphatemia, and renal toxicities are provided in Table 6-3. Refer to preclinical toxicity and or clinical data found in the [BGJ398 Investigator's Brochure].

6.3 Concomitant medications

The patient must notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications. If a drug is listed under "Permitted concomitant therapy requiring caution and/or action" and also under "Prohibited concomitant therapy", the drug should be prohibited.

6.3.1 Permitted concomitant therapy

Any palliative and supportive care for disease related symptoms, including any medication for a concurrent medical condition are permitted, except as specifically prohibited below.

Oral phosphate binders

Phosphate lowering treatment, including a low phosphate diet and phosphate binding therapy, such as sevelamer hydrochloride, should be implemented prophylactically at study drug initiation and modified as clinically indicated throughout BGJ398 administration. Recommendations for treatment are provided in Table 6-3, and should be modified as necessary as per country, package insert or institutional practice.

Hematopoietic growth factors

Hematopoietic growth factors (e.g., erythropoietin, G-colony stimulating factor (CSF) and GM-CSF) are not to be administered prophylactically or to be used to meet eligibility criteria. However, these drugs may be administered per the labeling of these agents or as dictated by local practice or guidelines established by the American Society of Clinical Oncology (ASCO).

Hormone replacement therapies

Hormone replacement therapies such as thyroid and growth hormones are allowed, as well as estrogen replacement hormone treatment.

6.3.2 Permitted concomitant therapy requiring caution and/or action

Drugs that alter the pH of the GI tract

BGJ398 is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of both compounds, and limit bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids**. Therefore, study drug(s) should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent**. Note that some proton-pump inhibitors may inhibit BCRP.

Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing drug exposure to sub-therapeutic levels. In addition BGJ398 is an in vitro inhibitor of CYP3A4 and has the potential to increase the systemic exposure of corticosteroids that are metabolized by CYP3A4.

Systemic corticosteroid treatment can be used with caution and minimized to the extent possible.

Substrates and inhibitors

CYP substrates and inhibitors

BGJ398 was shown to inhibit the cytochrome p450 isoenzyme CYP3A4 in *in-vitro* assays, thus, suggesting an increased risk of drug interactions with concomitant medications that are metabolized by CYP3A4. However, such interactions have not been confimed in patients. Therefore, investigators may administer medications that are known to be metabolized by CYP3A4. Patients must be monitored for potentiation of toxicity and may require dose titration or reduction of the CYP3A4 substrate. In particular caution is advised when substrates with a narrow therapeutic index, such as alfentanil, fentanyl, astemizole, cisapride, diergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus, and terfenadine need to be administered. Please refer to Appendix 1 for the list of medication to be used with caution.

Caution is advised when BGJ398 is co-administered with opioid analgesics. Inhibition of opioid metabolism by CYP3A4 can lead to opioid toxicity, including fatal respiratory depression, or an enhanced risk for QTc prolongation. Patients receiving BGJ398 and opioid analgesics should be carefully monitored. Synthetic opioids with clinically relevant interactions with CYP3A4 inhibitors include, but are not limited to, propoxyphene, fentanyl, alfentanyl and sufentanil. Use of alfentanyl, a sensitive CYP3A4 substrate with narrow therapeutic window, should be avoided whenever possible. The use of methadone and levomethadyl should also be avoided whenever possible. Refer to the Appendix 1 for the list of medications to be used with caution. Note that the list may not be comprehensive.

Hormonal contraceptives may be affected by cytochrome P450 interactions and are therefore not considered effective for this study. For allowed contraception methods please refer to Section 5.3. Highly effective contraception should be maintained throughout the study.

BGJ398 is a reversible inhibitor of CYP2C8, CYP2C9 and CYP2C19. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2C8, CYP2C9, CYP2C19, or those substrates that have a narrow therapeutic index.

BGJ398 is a substrate of CYP3A4. Therefore moderate inhibitors and inducers should be used with caution if no other alternative is available. Strong inhibitors and inducers are prohibited.

Please refer to the Appendix 1 for the list of medications to be used with caution. Please note that the list might not be comprehensive.

Transporter substrates

In vitro data show that BGJ398 is an inhibitor of BCRP. CQM157, a metabolite of BGJ398, is an inhibitor of transporters P-gp, BCRP, OATP1B1, and OATP1B3 (IC_{50} 2-4 µM). In the absence of data confirming whether transporter interactions occurs in vivo, patients receiving medications that are substrate of these transporters must be monitored for potential toxicity and may require dose titration or reduction of the medication.

Non-enzyme Inducing Anti-epileptic drugs (non-EIAED)

Non-enzyme inducing anti-epileptic medication (non-EIAED) such as valproic acid, levetiracetam and lamotrigine are allowed with caution. Patients who were previously on a non-EIAED and need to change anti-convulsants, should be started on another non-EIAED if at all possible. EIAEDs are not permitted (see Section 6.3.3 and Appendix 2).

Anti-emetics

Anti-emetics are allowed for the treatment of nausea or vomiting. It is recommended to avoid using drugs that are known to cause QT prolongation. Note that some anti-emetics have a known risk for Torsade do Pointes, and therefore need to be used with caution. See Appendix 1 for list of drugs that need to be used with caution. Aprepitant is both a sensitive substrate and a moderate CYP3A4 inhibitor and can be used with caution if an alternative is not available.

Possible and conditional risk of QT/QTc interval prolongation or torsade de pointes medications

There is no current evidence that BGJ398 has an effect on cardiac conduction or ECG intervals (see current version of the BGJ398 Investigator Brochure). However, medications that have the potential to prolong the QT/QTc interval or induce torsade to pointe (possible and conditional risk of TdP/QT prolongation) are allowed with caution. Investigators at their discretion may co-administer such medications, but patients should be carefully monitored. See Appendix 1 for list of drugs that need to be used with caution. Please note that the list might not be comprehensive.

6.3.3 Prohibited concomitant therapy

Other investigational and antineoplastic therapies

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic and/or radiation therapy other than the study treatments) must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study.

CYP inhibitors

Strong inhibitors of CYP3A4 such as the ones listed in Appendix 2 are prohibited because BGJ398 is a likely substrate of this isoenzyme. Caution should be used during administration of moderate inhibitors. The following food products are prohibited: Seville oranges or juice, grapefruit, grapefruit juice, grapefruit hybrids, and pummelos.

CYP inducers

Strong inducers of CYP3A4 are prohibited because their usage would likely decrease the exposure of BGJ398. Therefore, agents such as those listed in Appendix 2 are prohibited. Please note that the list may not be exhaustive.

Phosphorus and calcium

Medications that increase the serum levels of phosphorus and/or calcium are prohibited. These include, but are not limited to, calcium, phosphate, vitamin D, parathyroid hormone (PTH).

Known Risk of QT/QTc interval prolongation or torsade de pointes medications

There is no current evidence that BGJ398 has an effect on cardiac conduction or ECG intervals (See current version of the BGJ398 Investigator Brochure). However, medications that are known to prolong the QT/QTc interval or induce Torsade de Pointes (Risk of TdP/QT prolongation) are prohibited. List of these medications is given in Appendix 2. Please note that the list might not be comprehensive.Herbal medications

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

Enzyme Inducing Anti-epileptic drugs (EIAEDs)

Enzyme inducing anti-epileptic medication is not allowed (please refer to Appendix 2). Patients who were previously on a non-EIAED and need to permanently change anticonvulsants, but who cannot change to another non-EIAED must be discussed with Novartis. These patients will be taken off-study unless it is felt that they have benefited from the therapy following discussion with Novartis.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the Molecular pre-screening Informed Consent Form or Informed Consent Form for the Study, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

Once assigned, the Subject No. must not be reused for any other patient and the Subject No. for that individual must not be changed, even if the patient is re-screened.

6.4.2 Treatment assignment or randomization

The assignment of a patient to the treatment groups will be coordinated by Novartis. No randomization will be performed for this study.

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol. Study drug will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

BGJ398 will be provided by Novartis Pharma in hard gelatin capsules covering dosage strengths of 25 and 100 mg (expressed in mg of BGJ398 free base, open label bulk).

6.5.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient. Study drugs will be packed as open label supply which allows the patient to take medication at home.

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, BGJ398 should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Dosing data for BGJ398 will be recorded on the Dosage Administration eCRF.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging at the end of each cycle, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate

7 Visit schedule and assessments

7.1 Study flow and visit schedule

For all visits, there is a ± 3-day window on assessments to take into account scheduling over public or religious holidays, **if not explicitly specified otherwise**. [redacted] For imaging assessments, a ±7 day window is allowed, except for the first post baseline assessment and for confirmatory scans (+7 day window only permitted). All screening assessments, including baseline imaging assessments, must be completed within 28 days before the first dose, with the exception of the serum pregnancy test (β-hCG) that needs to be performed ≤ 72hrs before the first dose of study treatment. Every effort must be made to follow the schedule outlined in Table 7-1.

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

Molecular pre-screening assessments can be performed any time prior to the initiation of screening.

[redacted]

Assessments which are indicated to be performed at screening and on Cycle 1 Day 1, need only to be repeated at Cycle 1 Day 1 if screening assessment was more than 3 days earlier.

All assessments should be performed as outlined in Table 7-1 and as clinically indicated.

Table 7-1 Visit evaluation schedule

	Category	Reference to section	Molecular pre - screening	Screening	Pre-Surgical Treatment	Day of Surgery	Cycle 1					Cycle 2				Cycle 3		Subsequent cycles		End of study treatment	30 day Follow up	Disease Progression	Survival follow up
			Screening Phase		Surgical phase (Group 2)		Treatment Phase														Follow-up		
Day of cycle				**-28 to -1**	**1**	**5-10**	**6-11**	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**22**	**1**	**22**				
Informed consent for molecular pre-screening if applicable	D	7.1.1	X																				
Study Informed Consent (ICF)	D	7.1.2		X																			
[redacted]																							
Demography	D	7.1.2.3	X	X																			
Inclusion/exclusion criteria	D	7.1.2 and 5		X																			

	Category	Reference to section	Molecular pre - screening	Screening	Pre-Surgical Treatment		Day of Surgery	Cycle 1					Cycle 2				Cycle 3		Subsequent cycles		End of study treatment	30 day Follow up	Disease Progression	Survival follow up
			Screening Phase		Surgical phase (Group 2)			Treatment Phase														Follow-up		
Day of cycle				**-28 to -1**	**1**	**5-10**	**6-11**	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**22**	**1**	**22**				
Relevant medical history/current medical conditions	D	7.1.2.3		X																				
Diagnosis and extent of cancer	D	7.1.2.3		X																				
Prior antineoplastic therapy	D	7.1.2.3		X																				
Prior/ concomitant medications	D	6.3		X	X	X	X	Continuous													X	X		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.4																			X	X	X	X
Physical examination	S	7.2.2.1		X				X		X		X	X	X		X	X	X	X	X	X			
Height	D	7.2.2.3		X																				
Weight	D	7.2.2.3		X				X					X				X				X			
Vital signs	D	7.2.2.2		X				X		X	X	X	X	X	X	X	X	X	X	X	X			
Performance status	D	7.2.2.4		X				X				X	X			X	X		X		X			
Hematology	D	7.2.2.5.1		X				X					X				X		X		X			

	Category	Reference to section	Molecular pre - screening	Screening	Pre-Surgical Treatment		Day of Surgery	Cycle 1					Cycle 2				Cycle 3		Subsequent cycles		End of study treatment	30 day Follow up	Disease Progression	Survival follow up
			Screening Phase		Surgical phase (Group 2)			Treatment Phase														Follow-up		
Day of cycle				**-28 to -1**	**1**	**5-10**	**6-11**	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**22**	**1**	**22**				
Chemistry	D	7.2.2.5.2		X				X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Coagulation	D	7.2.2.5		X				If clinically indicated																
Urinalysis (microscopic or macroscopic)	D	7.2.2.5.3		X				If clinically indicated																
Pregnancy test	D	7.2.2.5		X				X					X				X		X		X			
Ophthalmologic assessment	D	7.2.2.8		X				X			X		X				X		X		X			
Tumor response per RANO v1.0 (* : within 72 hours of surgery)	D	7.2.1		X			X*	First post baseline scan occurs cycle 3 day 1; subsequent scans occur every 8 weeks until unacceptable toxicity or disease progression, whichever occurs first													X		X	
Surgery	D	4.1					X																	
Study drug administration		6.1			Continuous from day 1 till day of surgery			Continuous on a 3 weeks on 1 week off schedule																
12-Lead ECG (*pre-dose)	D	7.2.2.7		X	X*		X	X*					X*				X*		X*		X			

	Category	Reference to section	Molecular pre - screening	Screening	Pre-Surgical Treatment		Day of Surgery	Cycle 1					Cycle 2				Cycle 3		Subsequent cycles		End of study treatment	30 day Follow up	Disease Progression	Survival follow up
			Screening Phase		**Surgical phase (Group 2)**			**Treatment Phase**														**Follow-up**		
Day of cycle				**-28 to -1**	**1**	**5-10**	**6-11**	**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**22**	**1**	**22**				
[redacted]																								
Adverse events (* SAE only)	D	7.2.2	X*	X	X	X	X	Continuous													X	X		
[redacted]																								
Survival follow up	D	7.1.5																						X

7.1.1 Molecular pre-screening

[redacted]

Local pre-screen

If local testing will be conducted to determine the molecular status of the tumor, potential patients will be asked to sign a "Pre-screening Informed Consent" to allow for the collection and analysis of the sample.

A consent form is not needed if the molecular status of the tumor was previously determined. Evidence of local data must be present in the source documentation.

[redacted]

7.1.2 Clinical Screening

The IRB/IEC study approved informed consent form (ICF) must be signed and dated before any screening procedure is performed. Procedures which are part of the clinical routine during the initial diagnostic work-up of the patient may be obtained before obtaining the ICF. A copy of the ICF must be given to the patient or to the person signing the form. The investigator or designee must record the date when the study informed consent was signed in the medical records of the patient.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1. Screening assessments must be completed within 28 days prior to the first dose of treatment with the exception of the serum pregnancy test (β-hCG) that needs to be performed ≤ 72hrs before the first dose of study treatment. Clinical and radiological tumor assessment (RANO criteria) should be conducted preferably within 1 week (7 days) prior to the first dose of the study drug; however tumor assessments up to 4 weeks (28 days) prior to the first dose will be acceptable. Screening assessments must be repeated if >28 days from Cycle 1 Day 1.

7.1.2.1 Enrollment process

After the patient has signed an ICF to participate in the treatment phase of the study, an enrollment form detailing the patient's age, gender, disease type, screening date, and required genetic alteration, as well as the anticipated date of first study drug treatment. The enrollment form will be faxed or e-mailed to the Novartis Clinical Trial Lead or his/her designee for approval and acknowledgement of patient inclusion.

7.1.2.2 Information to be collected on screening failures

Patient who

- signed a molecular pre-screening ICF but are considered as ineligible after molecular screening
- are found not eligible to participate in the treatment phase of the study, after signing the informed consent form
- are not started on study treatment based on the opinion of the investigator
- withdraw consent prior to initiating study drug

will be considered as screening failures, and data will be handled in the same manner. The molecular pre-screening failure or screening failure will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure subjects. No other data will be entered in the database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the screening phase (see Section 8 for SAE reporting details).

The following data must be collected in the source documents for any patient who signs an ICF:

- Informed consent information
- Inclusion/exclusion
- demography
- Screening log page (including reason for not being started on treatment)
- Serious Adverse Event (see Section 8 for SAE collection, requirements and reporting)

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, prior concomitant medications, diagnosis and extent of tumor, baseline tumor mutation status (gene amplification or translocation) and details on prior antineoplastic treatments.

7.1.3 Treatment period

During the treatment period, the patient is obliged to follow the investigators instructions with regards to contraception, concomitant medications and dosing regimen. There is no fixed duration; patients may continue treatment with the study drug until the development of an unacceptable toxicity that precludes any further treatment, disease progression, and /or treatment is discontinued at the discretion of the Investigator or by patient refusal.

For the patients included in group 2 (surgical group), there is a fixed treatment duration of 5 to 10 days before surgery. The last dose should be on the day of surgery, or the day before at the discretion of the investigator. At a minimum of 2 weeks post-surgery, patients may resume study treatment with BGJ398 until experiencing unacceptable toxicity, disease progression and/or the treatment is discontinued at the discretion of the investigator or by patient refusal (withdrawal of consent). Day 1 of treatment following surgery will be considered to be Cycle 1 Day 1. For details of assessments during the treatment period, refer to Table 7-1.

7.1.4 End of treatment visit including study completion and premature withdrawal

At the time patients discontinue study treatment, a visit should be scheduled within 14 days, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. An **End of Treatment Phase Disposition** CRF page should be completed, giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted to return 30 days after the last administration of the study treatment.

In addition, patients who discontinue study treatment for any reasons other than disease progression, death, or withdrawal of study consent, should also return for disease follow-up and will be followed for survival (please refer to Section 7.1.5) and should not be considered withdrawn from the study. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to obtain the follow-up information.

If a patient discontinues study treatment, but continues study assessments in the follow-up period, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the **Study Phase Completion Disposition** CRF page.

7.1.4.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Unacceptable AE(s)
- Delay in dosing > 14 consecutive days (unless agreed otherwise between Novartis and the Investigator.
- Pregnancy of the patient
- Patient withdrew consent
- Lost to follow-up
- Disease progression (clinical or radiological)
- Initiation of new cancer therapy

Note: refer to Section 7.1.5 for the requirement to further follow patients after discontinuation of study treatment.

7.1.4.2 Replacement policy

No replacement will be needed.

7.1.5 Follow up period

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

30-day safety follow-up period

All patients must complete the safety follow-up assessments 30 days after the last dose of the study treatment.

All AEs suspected to be related to study drug should be followed up weekly, or as clinically indicated, until resolution or stability (see also Section 6.2.2).

Disease progression follow-up period

All patients enrolled in the study who discontinue study treatment for any reason other than disease progression will be followed up monthly via a phone call and will have MRI scan (or CT if the patient cannot tolerate MRI) every 8 weeks (± 7 days) as detailed in Table 7-1, until disease progression or the initiation of subsequent anticancer therapies, or death, whichever occurs first.

Survival follow-up period

All patients enrolled in the study will be followed for survival every 4 months for at least one year per e.g., phone call, after LPLT. Possible newly started antineoplastic therapies during this FU period must be recorded on the Antineoplastic therapy since discontinuation eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response and progression will be assessed by the Investigator, using the Response Assessment in Neuro-Oncology (RANO) Working Group (Wen et al. 2010) as detailed in Appendix 3.

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.

For group 1, the baseline scan must occur within 28 days of treatment initiation. For group 2, patients undergoing surgery, per standard of care, a MRI should be performed within 72 hours after surgery (Wen et al. 2010). This scan can function as the baseline scan if BGJ398 therapy is initiated within four weeks of surgery. If BGJ398 is initiated after 4 weeks following surgery, a baseline scan must be performed within 7 days of starting BGJ398. Subsequent post baseline scans will be performed as described above. For group 2 patients who do not undergo surgery the baseline scan will be defined as per group 1.

Note: in case a patient cannot tolerate MRI, the patient may still participate in the study following discussion between Novartis and the investigator. In this case, all efficacy assessments will be made by CT scans for that patient. Efficacy assessments should be performed by using the same technique throughout the study for each patient.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing the procedures listed below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination must be performed as indicated in Table 7-1.

Physical examination will be performed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

Physical examination will be performed according to the standards at each institution.

Information about the physical examination must be present in source documentation at the study site. Significant findings that are present prior to signing of informed consent form for the study must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent for the study must be recorded on the AE eCRF.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before dosing and as indicated in Table 7-1.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

7.2.2.3 Height and weight

Height and body weight will be measured. Weight will be measured as indicated in Table 7-1. Height will be collected at screening only. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

7.2.2.4 Performance status

The ECOG performance status (please refer to Table 7-2) will be assessed as indicated in Table 7-1. Assessment via Karnofsky Performance Scale is acceptable but requires subsequent conversion to ECOG (Ma et al, 2010) before being reported on the e-CRF. Assessments of performance status will be performed on the scheduled day, even if study treatment is being withheld.

Table 7-2 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 eCRF page.

7.2.2.5 Laboratory evaluations

Clinical laboratory analyses are to be performed by the local laboratory as indicated in Table 7-1 and Table 7-3. Laboratory tests will be collected and analyzed on the scheduled day, even if study treatment is being withheld. More frequent assessments may be performed at the discretion of the Investigator and if medically indicated, and should be recorded on the Unscheduled Visit eCRFs.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the Adverse Events eCRF page. Laboratory data will be summarized using the CTCAE (version 4.03).

Novartis must be provided with a copy of the laboratory's certification, and normal ranges for each parameter measured. In addition, if at any time a patient has laboratory parameters

obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and normal ranges for that laboratory.

Table 7-3 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Biochemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Calcium (Total), Chloride, Creatinine, Blood Urea Nitrogen (BUN) or Urea, Potassium, Sodium, Magnesium, Inorganic Phosphorous . Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, direct/indirect bilirubin, Total Protein, Uric Acid, Amylase, Lipase.
Urinalysis	Macroscopic Panel (Dipstick) (Blood, Glucose, Ketones, pH, Protein, Specific Gravity). Microscopic Panel (Red Blood Cells, WBC).
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), Partial thromboplastin time (PTT),
Pregnancy Test	Serum hCG at screening; EOT and other times points serum hCG or urine.

7.2.2.5.1 Hematology

Hematology tests are to be performed by the local laboratory according to the Visit Schedules outlined in Table 7-1 and Table 7-3.

7.2.2.5.2 Clinical chemistry

Clinical chemistry tests are to be performed by the local laboratory according to the Visit Schedule outlined in Table 7-1. For details on the Biochemistry panel refer to Table 7-3. Assessment of inorganic phosphorus will be performed as part of the chemistry analysis, or as indicated in Table 7-1.

- On Cycle 1, Day 1, 8 hours post dose, inorganic phosphorous will be the only test conducted of the chemistry panel.
- On Cycle 1, Day 2, inorganic phosphorous will be the only test conducted of the chemistry panel.

7.2.2.5.3 Coagulation

International normalized INR, pro-thrombin time (PT), partial thromboplastin time will be measured according to the visit schedule in Table 7-1 and Table 7-3.

7.2.2.5.4 Urinalysis

Dipstick Urinalysis will be conducted as directed in Table 7-3 on the days outlined in Table 7-1 or as clinically indicated, within the windows outlined in Section 7.1. Any significant findings on dipstick will be followed up with a microscopic evaluation (listed in Table 7-3) where WBC and RBC sediments will also be measured.

7.2.2.5.5 Pregnancy and assessments of fertility

All women of childbearing potential (pre-menopausal or less than 1 year after the onset of menopause) must have a serum pregnancy test (β-hCG) ≤ 72 hrs before the first dose of study treatment. Additionally, a serum or urine pregnancy test should be performed at Day 1 of each cycle and at the End of Treatment visit.

A positive pregnancy test requires immediate interruption of study drug treatment until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the study. See Section 8.4 for pregnancy reporting.

7.2.2.6 Radiological examinations

7.2.2.6.1 MRI scan (or CT if patient is unable to undergo MRI).

Please refer to details in Section 7.2.1 and Appendix 3. The same modality (MRI/CT) must be used throughout the study

First post baseline scan occurs cycle 3 day 1; subsequent scans occur every 8 weeks until unacceptable toxicity or disease progression, whichever occurs first.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed

- at screening
- pre-dose, on D1 of every cycle. For Cycle 1 Day 1 pre-dose ECG, the QTcF value must be within eligibility criteria prior to study drug treatment.
- Surgical group (group 2) : pre-dose on D1, and on the day of surgery
- at the EOT visit

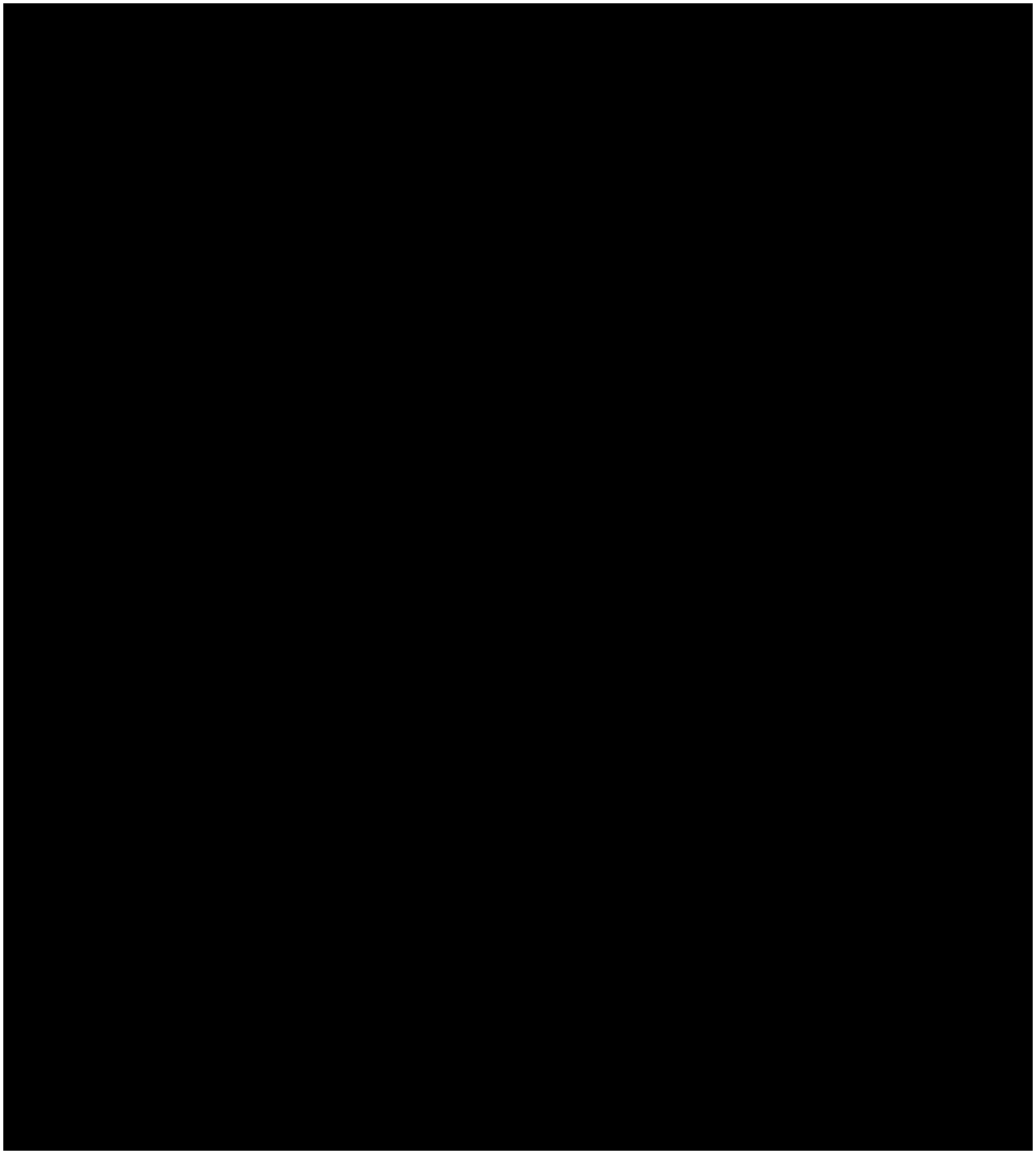
A standard of 12-Lead ECG that monitors QTcF interval, heart rate, PR interval, uncorrected QT interval, and QRS duration will be performed as indicated in in Table 7-1.

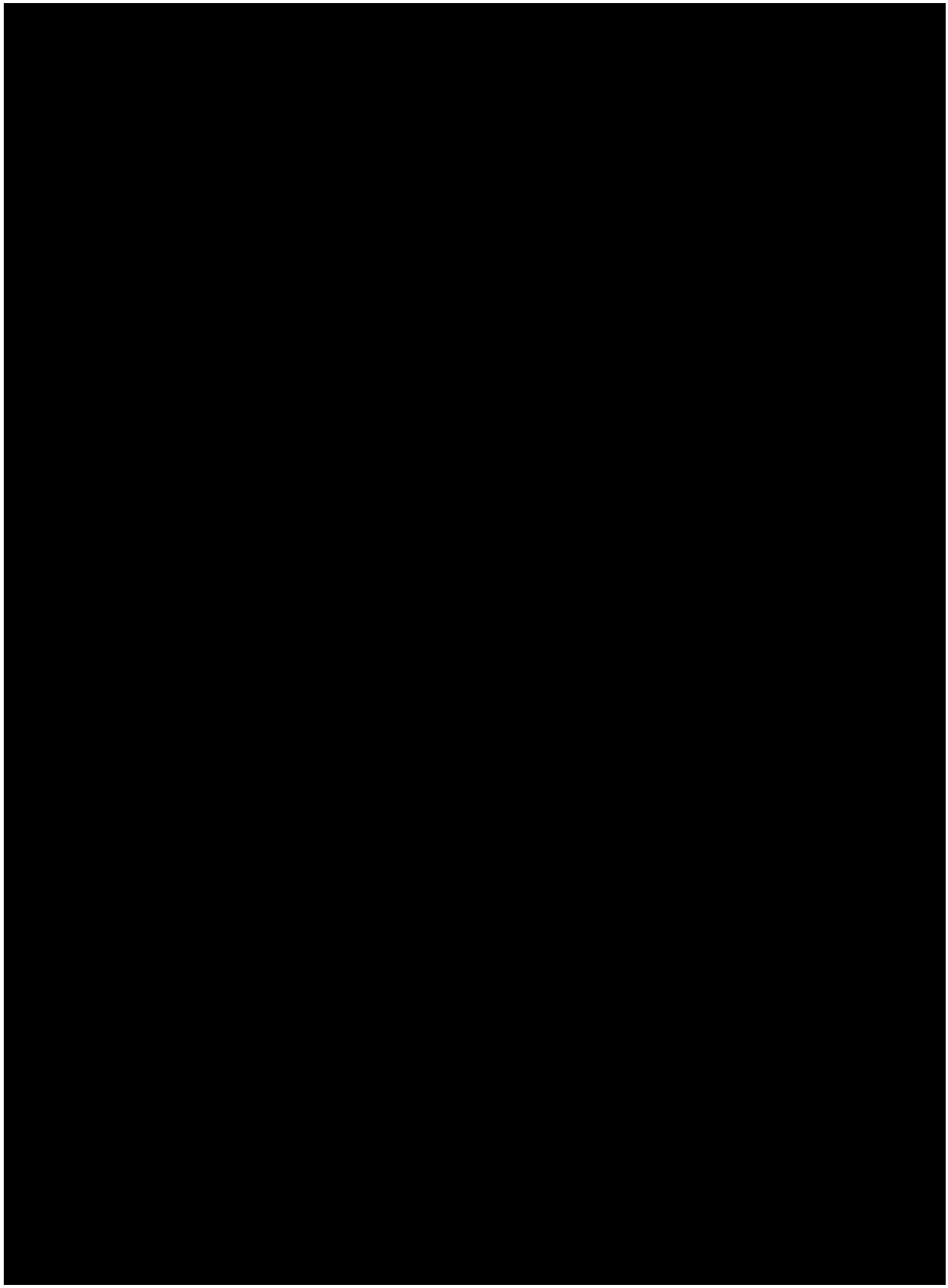
Interpretation of the tracing must be made by a qualified physician at the site and documented on the ECG eCRF. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Relevant Medical History/Current Medical Conditions eCRF. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the AE eCRF.

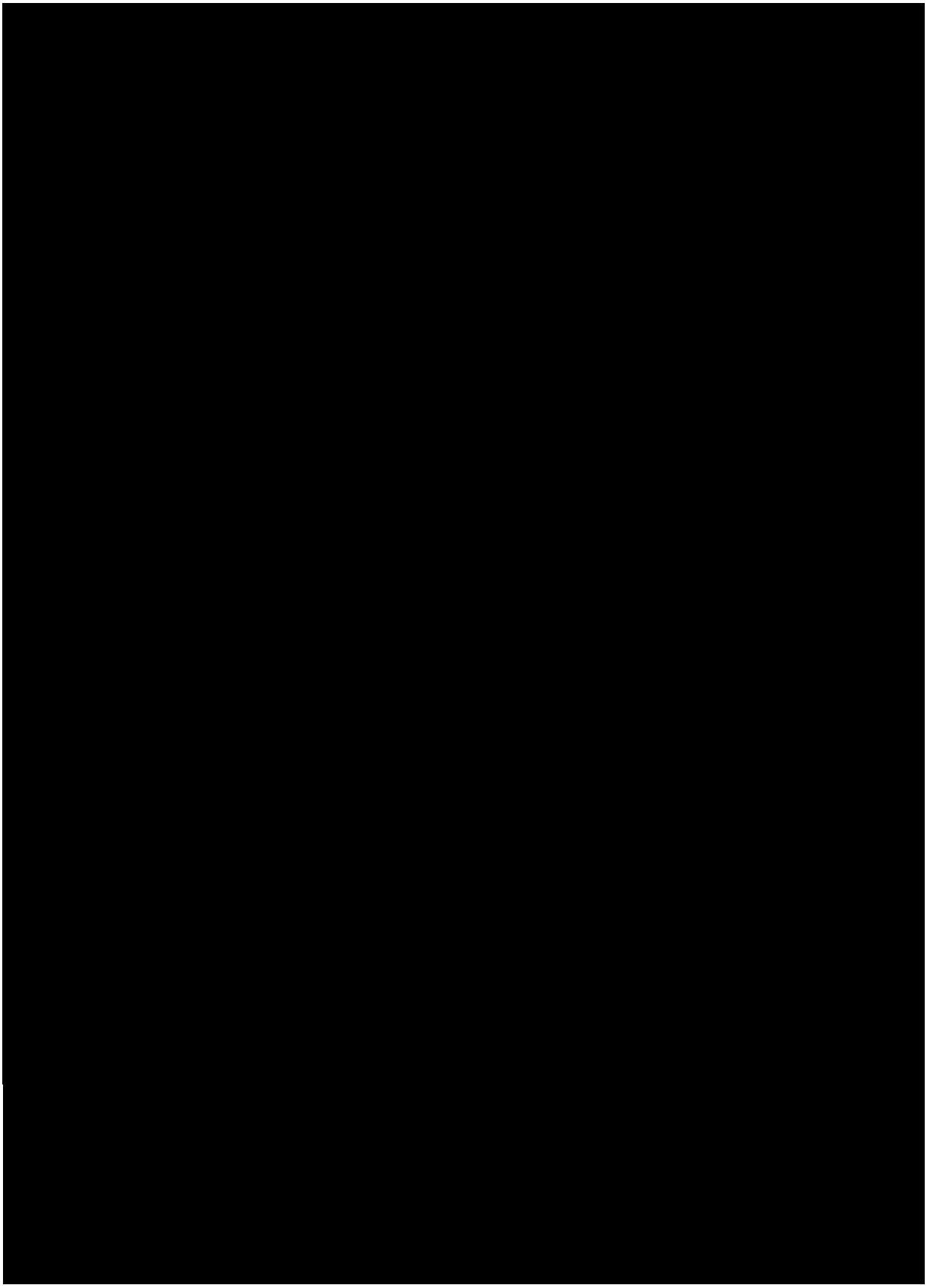
[redacted]

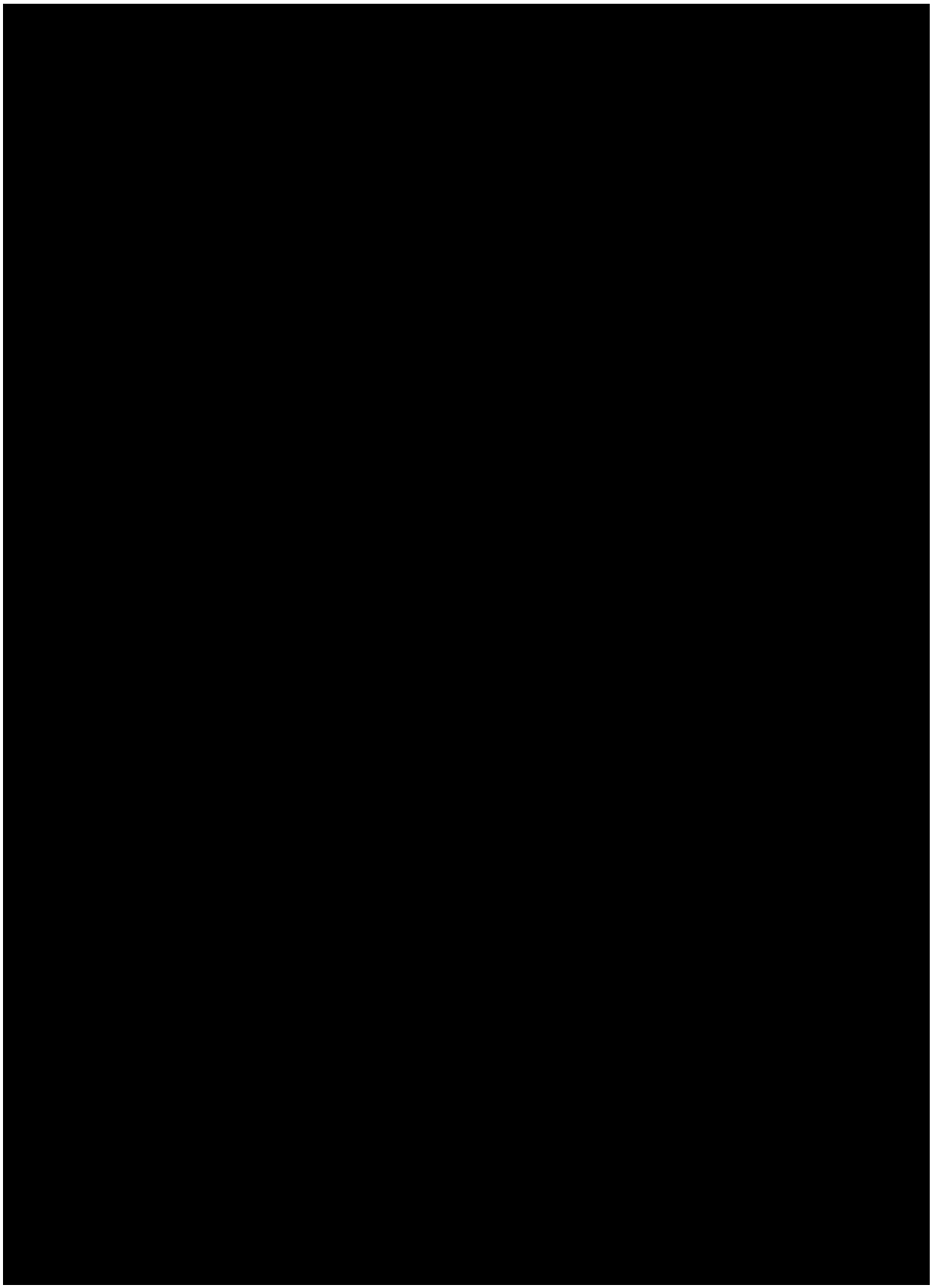
7.2.2.8 Ophthalmologic assessments

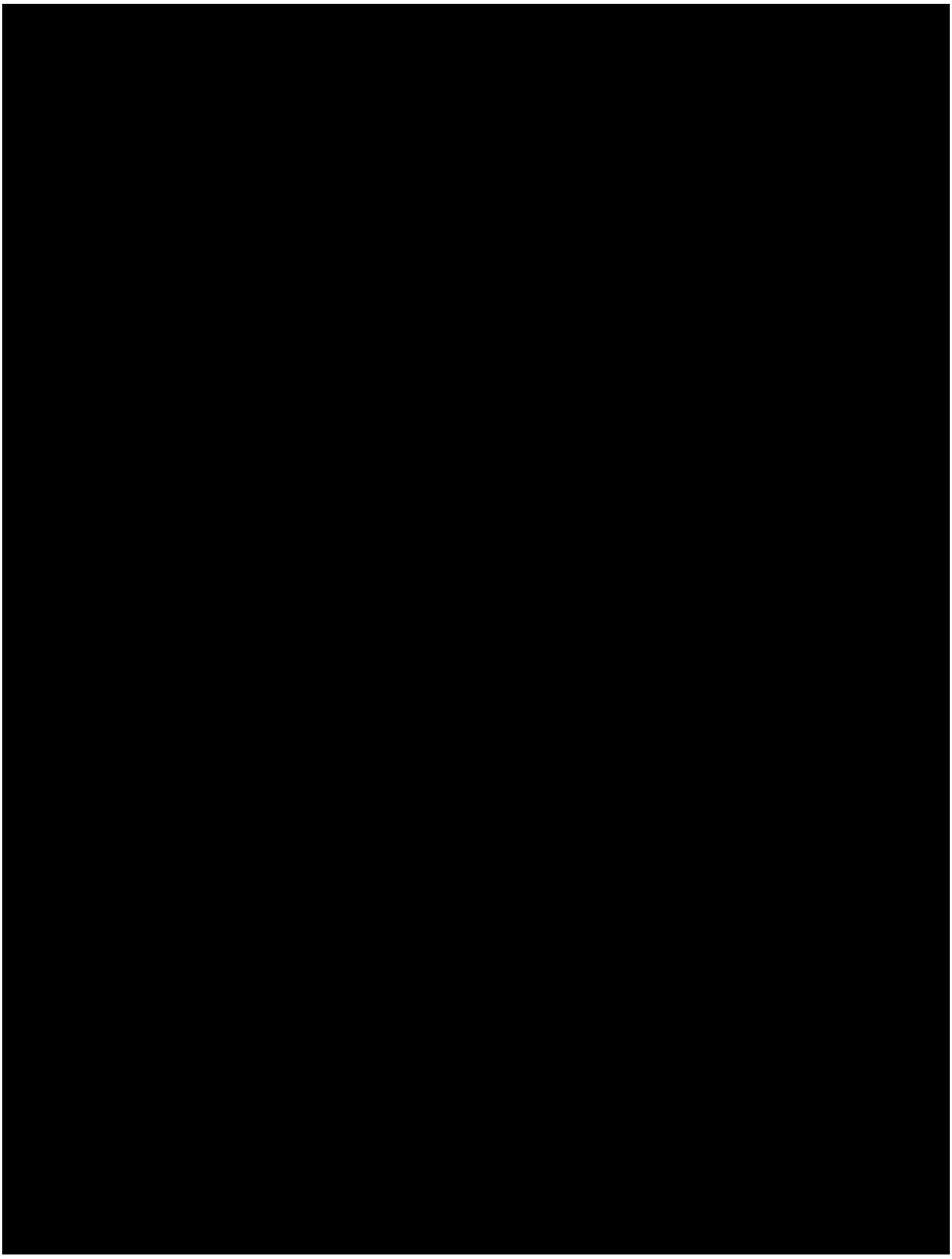
Ophthalmologic examinations will be performed as indicated in Table 7-1 and includes: visual acuity testing, slit lamp examination of the anterior eye segment, intraocular pressure (IOP), and fundoscopy. Additional examination methods such as specular microscopy (that enables a magnified, direct view of the corneal endothelium), corneal pachymetry, and dilated fundoscopy will be performed as clinically indicated.











8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

[redacted]

AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g., an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

[redacted]

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events 4.03 version unless otherwise specified.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates) or Ongoing at End of Study
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered / not resolved, recovered / resolved, recovering / resolving, recovered / resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a SAE is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

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

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

Whenever possible, a diagnosis should be reported instead of underlying signs and symptoms.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Here as well, whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by

the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

[redacted] SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g., an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedure.

[redacted] SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE

occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

Serious adverse events considered by the Investigator to be possibly related to a biopsy procedure will be indicated as such in the AE eCRF. This information will be followed for 30 days after the biopsy procedure.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational/study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be in place for this trial. However, measures are put in place for monitoring the safety of the patients participating in this part of the study, and Novartis will convene a joint teleconference with the participating Investigators to ensure a prompt review of safety data and constant monitoring for emerging safety signals by participating study sites and Novartis Personnel. As for any other study conducted by Novartis, any SUSAR and/or new safety signals will be promptly communicated to all participating investigators and Health Authorities.

Individual patient data will be reviewed on an ongoing basis and aggregate safety data and the primary endpoint will be monitored by the study team after every 8th patient completes the first cycle of treatment or discontinues the study, whichever occurs first. The data review and analysis will be based on the available investigator reported data in the clinical database at the respective time.

8.7 Steering Committee

A Steering Committee constituted of members of the Oncology Translational Medicine Leadership Team will be formed for this study. If the monitoring of the study data require a decision to be taken on the continuation of the study, then the relevant data will be communicated to the Steering Committee for decision making purposes.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g., has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If te site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subjects initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they

have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into the CRF is complete, accurate, and that entry and updates are performed in a timely manner.

[redacted]

Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF (and/or designated laboratory requisition forms that are printed on 2 or 3-part, non-carbon-required paper). Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff; and one copy will be retained at the investigational site.

9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Relevant Medical history/Current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements [redacted] using descriptive statistics (quantitative data) and contingency tables (qualitative data). For all analyses, data from both treatment groups (surgical group and non-surgical group) will be pooled together, unless otherwise stated.

The analysis of study data will be based on all patients' data up to the time when all patients have potentially completed at least 6 cycles of treatment or discontinued the study. . This will be the cut-off point for the primary clinical study report (CSR). The additional data for any patients continuing to receive BGJ398 beyond the cut-off point for the primary clinical study report, as allowed by the protocol, 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 first dose of study treatment, whichever occurs first.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) includes all patients who received at least one dose of BGJ398. Patients will be classified according to the planned treatment. 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.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of BGJ398 and have at least one valid post-baseline safety assessment. Patients with FGFR1, 2, 3 and 4 amplifications enrolled prior to protocol amendment 2 will be included in the safety set. These patients will be included in the FAS and their data will be listed and summarized as described below, however they will not be part of the per-protocol set which will be used for the primary analysis.

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

Patients will be classified according to treatment received, where 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.

10.1.3 Per-Protocol Set

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 Clinical Study Protocol (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 major protocol deviations.

All major protocol deviations leading to exclusion from the PPS will be detailed in the Reporting and Analysis Plan (RAP).

10.1.4 Dose-determining analysis set

Not applicable

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study Treatment

The actual dose and duration in days of BGJ398 treatment as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized by means of descriptive statistics. The summary data will be presented for all study days as a single category. The total daily doses of BGJ398 for each patient will be summarized using descriptive statistics. The FAS will be used.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will be listed by patient and summarized by ATC (Anatomical therapeutic chemical classification system) term and dose group by means of contingency tables.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized by treatment group. Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions, see Section 10.5.

10.4 Primary objective

10.4.1 Variable

Preliminary tumor activity will be assessed using RANO criteria (Appendix 3) .

Six month progression free-survival (PFS6) rate will be the primary efficacy variable.

For patients in group 1 (non-surgical), 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.

For patients in group 2 ,who undergo surgery, 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.

For patients in group 2, who do not undergo surgery, PFS is defined as the number of days from first day of treatment to the first documented disease progression or date of death, whichever occurs first.

Patients in group 2, who undergo surgery but do not receive at least one post-surgical dose of BGJ398 (i.e., C1D1) will be excluded from the primary efficacy analysis; their data will be listed.

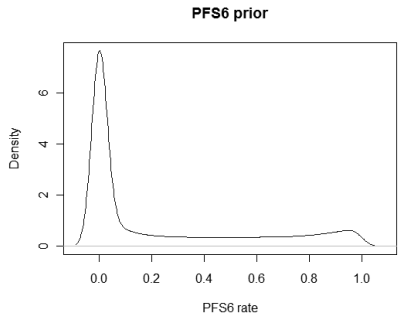
The Primary Analysis will be performed on the PPS (24 patients) and the FAS summary will be provided as a supportive analysis (34 patients). The labs, safety, [redacted] etc, data for the patient with amplifications using the FAS will be summarized, but the efficacy focus will be on the PPS.

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.

10.4.2 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 10-1 below).

Figure 10-1 PFS6 prior distribution



The prior 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 as described above. 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 (Clarke et al, 2011). 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%).

An interim analysis for futility will be conducted for patients in the PPS. Please see Section 10.7 for details.

10.4.3 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.

Other missing data will simply be noted as missing on appropriate tables/listings.

10.4.4 Supportive analyses

The supportive analysis will be done using the FAS following the statistical methodology as presented in Section 10.4.2. As a supportive analysis, Kaplan-Meier estimates of the PFS rate at 4, 6 and 12 months will be derived together with 95% confidence intervals. PFS will also be presented descriptively using Kaplan Meier plots. This analysis will be done for all patients in both the treatment groups pooled together and for the PPS and FAS seperately. This analysis

will be repeated on the subgroups of patients defined by previous bevacizumab treatment use and by treatment group, if the number of patients in each group allows for meaningful interpretation.

The primary analysis will be repeated on the subgroups of patients defined by previous bevacizumab treatment use and by treatment group, if the number of patients in each group allows for meaningful interpretation.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

Objective Response Rate

A secondary objective of the study is to assess preliminary anti-tumor activity of the BGJ398 using objective response rate (ORR) as the endpoint.

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 (Appendix 3).

The ORR analysis will include patients from the FAS who have measurable disease (as per RANO) at their baseline scan (as defined in Section 7.2.1). 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.

Overall Survival

For patients in group 1, 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.

For patients in group 2, who undergo surgery, 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.

For patients in group 2, who do not undergo surgery, OS is defined as the number of days from first day 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.

Patients in group 2, who undergo surgery but do not receive at least one post-surgical dose of BGJ398 (i.e., C1D1) will be excluded from the overall survival analysis; their data will be listed.

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. All patients in the FAS except patients in group 2, who undergo surgery but do not receive at least one post-surgical dose of BGJ398 will be included in this analysis.

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

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

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.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03 laboratory data will be graded accordingly. For laboratory tests covered by CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges, or alternative clinically meaningful limits.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots may be specified in the RAP.

10.5.3.4 Other safety data

Data from other tests (e.g., electrocardiogram or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration. Additionally, the following outputs will be produced:

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

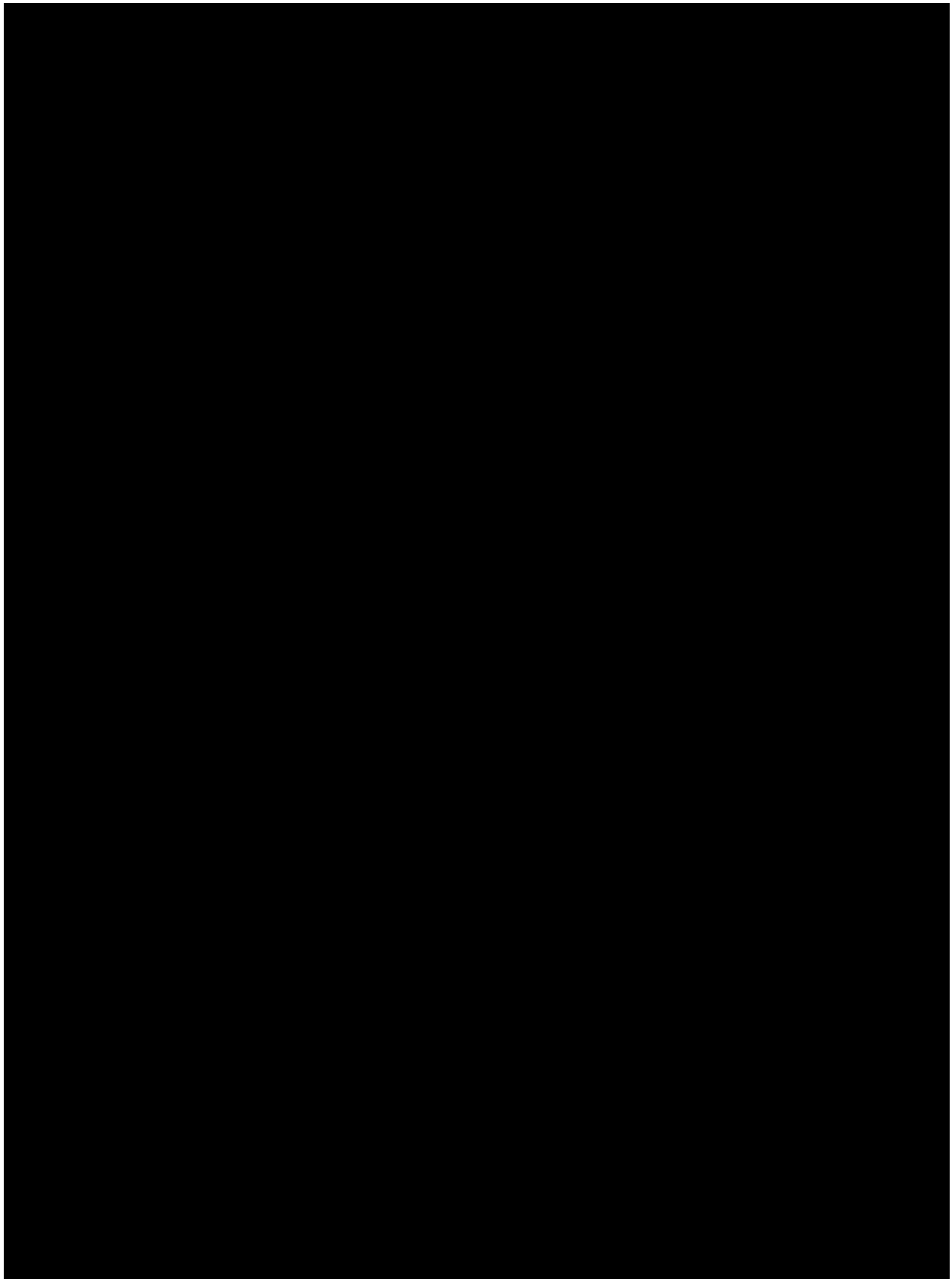
- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

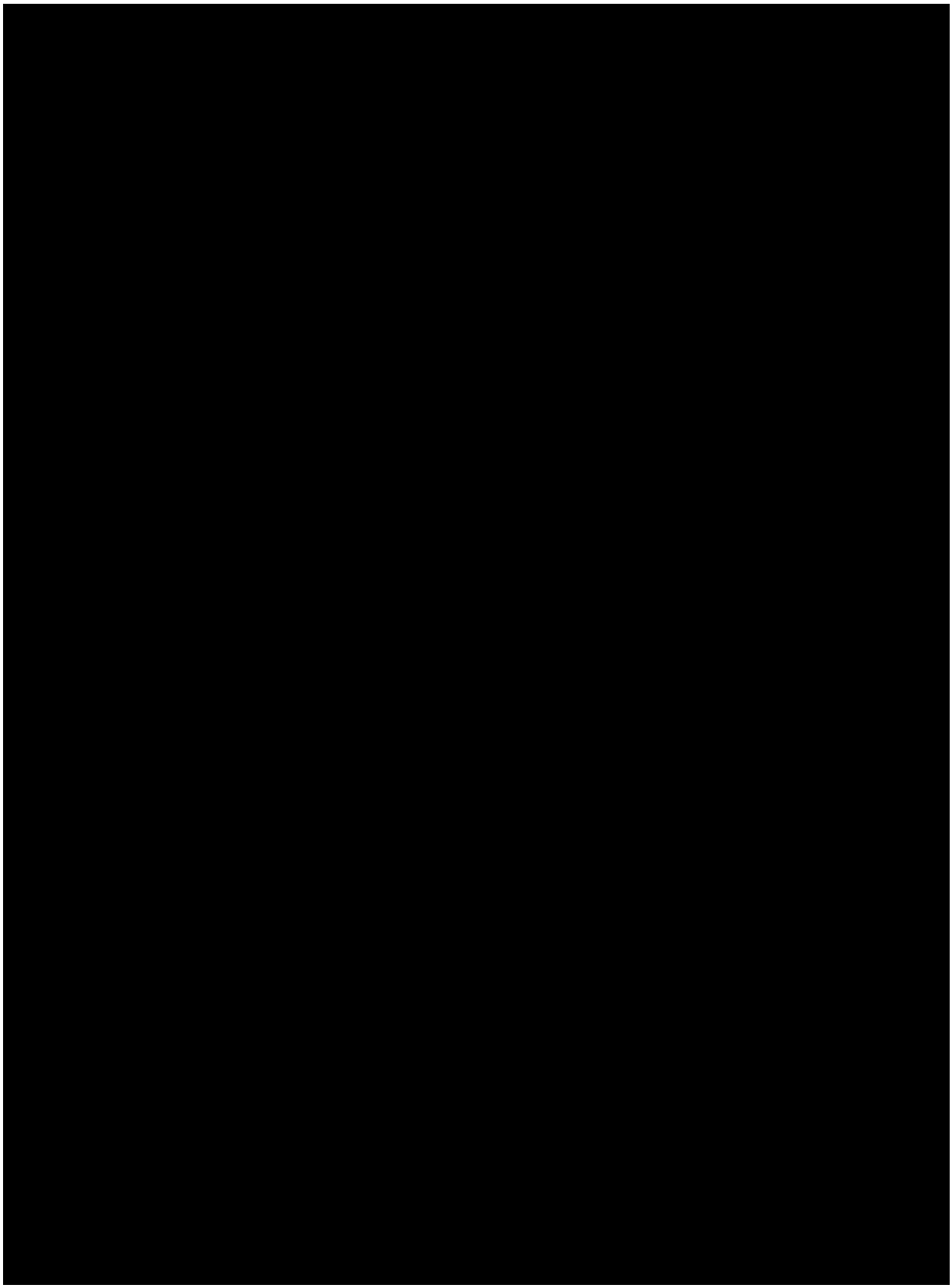
Ocular

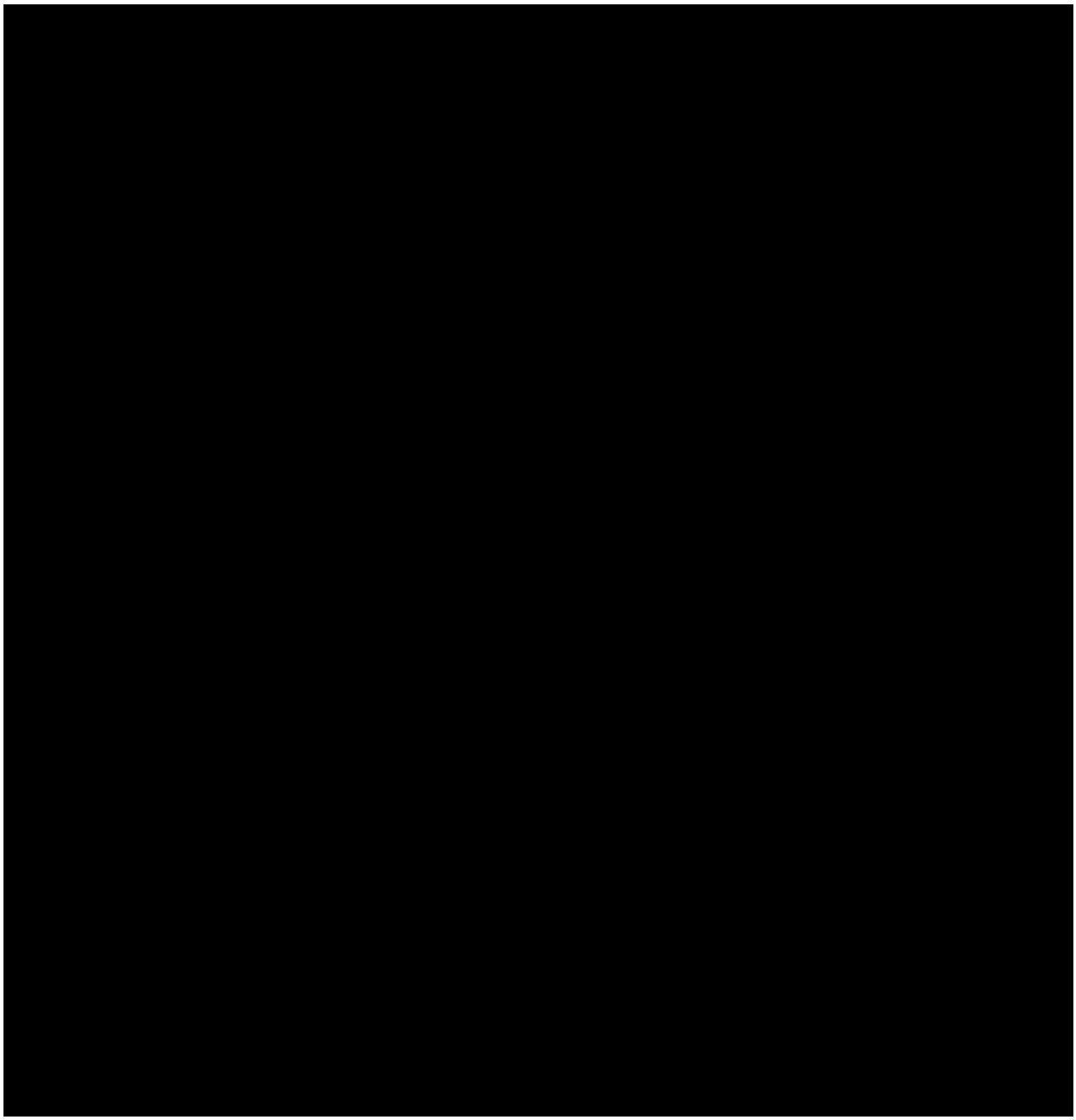
- Table with frequency of ocular events by cycle will be produced by treatment group.
- Listing of ocular assessments for all patients with at least one abnormality.

10.5.3.5 Tolerability

Tolerability of study drug will be assessed by summarizing the number of dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by patient and summarized. Cumulative dose, dose intensity and relative dose intensity of BGJ398 will be listed by patient and summarized. Categories for relative dose intensity of BGJ398 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented.







10.7 Interim analysis

An interim analysis for futility will be carried out once 10patients in the PPS have completed 6 cycles of treatment or discontinued earlier. The analysis will follow the methodology described for the primary efficacy analysis. If the following criterion is met, recruitment will continue, otherwise recruitment will be stopped:

Prob (PFS6 > 16%) > 80% and Prob (PFS6 > 25%) > 50%

This rule corresponds to approximately 16% predictive probability of success (assuming only administrative censoring at the time of data cut-off for interim analysis, and therefore using a beta-binomial distribution for calculating the predictive probability of success). In other words,

given the data at interim, if the predictive probability that the study will have a success at the final analysis is less than 16%, this study will be stopped at the interim for futility.

10.8 Sample size calculation

The operating characteristics of the design (with the primary analysis using PPS) have been assessed via simulations (see Table 10-2 below). 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 > 16%) > 80% and Prob (PFS6 > 25%) > 50% at the interim analysis and Prob (PFS6 > 25%) > 80% and Prob (PFS6 > 40%) > 50% at the final analysis.

Table 10-2 Operating characteristics of study design (primary analysis – 24 evaluable patients in PPS)

	True PFS6					
	0.16	**0.25**	**0.35**	**0.4**	**0.45**	**0.5**
Prob. of stopping at interim	0.816	0.521	0.26	0.143	0.068	0.039
Average sample size	12.576	16.706	20.304	31.998	23.048	23.454
Prob. of success (final)	0.000	0.026	0.229	0.465	0.708	0.861
Average study duration (months)	15.855	21.12	25.19	27.58	28.76	29.39

Assuming a true PFS6 rate of 50% and a uniform accrual of one patient per month, with 24 evaluable patients in the PPS (~17 PFS events), there is about 86.1% chance to achieve success at the end of the study.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors,

Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with [Section 4.9 of the ICH E6 GCP], and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be

maintained by the system. The investigator should retain records of the changes and corrections to CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial [ICH E6 Section 8] and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Novartis provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed

according to local regulations (e.g., UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1: List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or BGJ398.

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: 29 Oct 2012), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft guidance.

Table 14-1 Drugs to be used with caution while on the study

Category	Drug Names
Sensitive CYP3A Substrates	Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, indinavir, levomethadyl, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simvastatin, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc
Moderate inhibitors of CYP3A4	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, imatinib, Schisandra sphenanthera, tofisopam, verapamil
Moderate inducers of CYP3A4	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
Medications which alter the pH of the GI tract[1]	Proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids.
Medications that have possible risk of TdP/QT prolongation	Dronedarone, eribulin, lapatinib, sunitinib, nilotinib, tamoxifen, gatifloxacin, gemifloxacin, levofloxacin, ofloxacin, roxithromycin, telithromycin, clozapine, iloperidone, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, dolasetron, granisertron, ondansetron, escitalopram, venlafaxine, Ranolazine, voriconazole, amantadine, foscarnet, isradipine, moexipril, nicardipine, fingolimod, tacrolimus, atazanavir, felbamate, famotidine, fosphenytoin, alfuzosin, chloral hydrate, indapamide, lithium, octreotide, pasireotide, oxytocin, ranolazine, tizanidine, vardenafil
Medications that have conditional risk of TdP/QT prolongation	Amisulpride, amiptriptyline, clomipramine, desipramine, doxepin, fluoxetine, imipramine, nortriptyline, paroxetine, protriptyline, sertraline, trazodone, trimipramine, ciprofloxacin, trimethoprim-sulfa, diphenhydramine, fluconazole, itrazonazole, ketoconazole, ritonavir, galantamine, solifenacin
BCRP substrates	Rosuvatstatin, methotrexate, irinotecan, atorvastatin, simvastatin, topotecan, sulfasalazine

Category	Drug Names
[1] BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.	
Reference:	
FDA Guidance for Industry, Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Accessed 10 November 2013 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf.	
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Drug-Drug Interactions (DDI) Database: Novartis Oncology Clinical Pharmacology Internal Memorandum, Final (v04), 12-Oct-2012	

14.2 Appendix 2: List of prohibited medication

Table 14-2 List of prohibited medication while on the study

Category	Drug Names
Strong inducers of CYP3A4	Avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort
Strong Inhibitors of CYP3A4	Clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, voriconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, grapefruit juice, juice from Seville oranges, star fruits, pomegranates and pummelos.
Medications which increase serum phosphorus and/or calcium	Calcium, phosphate, vitamin D, parathyroid hormone (PTH)
Narrow Therapeutic index substrates of CYP3A4	Quinidine, astemizole, terfanadine, cyclosporine, sirolimus, tacrolimus, diergotamine, cisapride, ergotamine, pimozide, alfentanil, fentanyl thioridazine, diergotamine, dihydroergotamine, ergotamine
Medications with established potential for QT prolongation or Torsades de pointes	Amiodarone, Anagrelide, Arsenic trioxide, Astemizole (Off US mkt), Azithromycin, Bepridil (Off US mkt), Chloroquine, Chlorpromazine, Cisapride (Off US mkt), Citalopram, Clarithromycin, Cocaine, Disopyramide, Dofetilide, Domperidone (Not on US mkt), Dronedarone, Droperidol, Erythromycin, Escitalopram, Flecainide, Grepafloxacin (Off market worldwide), Halofantrine, Haloperidol, Ibutilide, Levofloxacin, Levomethadyl (Off US mkt), Mesoridazine (Off US mkt), Methadone, Moxifloxacin, Ondansetron, Pentamidine, Pimozide, Probucol (Off US mkt), Procainamide (Oral off US mkt), Quinidine, Sevoflurane, Sotalol, Sparfloxacin (Off US mkt), Sulpiride (Not on US Mkt), Terfenadine (Off US mkt), Thioridazine, Vandetanib

Table 14-3 EIAEDs that are prohibited

Strong CYP3A inducers	**Moderate CYP3A inducers**
carbamazepine	felbamate
phenobarbital	topiramate (>200 mg/day)
phenytoin	oxcarbazepin
fosphenytoin	eslicarbazepin
primidone	rufinamide

14.3 Appendix 3: Response assessment in neuro-oncology (RANO) criteria

Antitumor response will be evaluated by the Response Assessment in Neuro-Oncology (RANO) working group (Wen et al 2010) criteria in this study. The RANO Criteria updates its established predecessor, the modified Macdonald Criteria (Macdonald et al 1990), by adding assessment of non-enhancing lesions and incorporating issues of pseudoprogression.

Patients will undergo MRI assessments for response evaluation on an approximately every 8 weeks interval from the start of the study until disease progression, as outlined in the Visit schedule Table 7-1.

The following components will be taken into account when assessing a patient's overall response at an individual evaluation.

- Tumor evaluation eCRF for measureable enhancing lesions (T1-Gd+)
- Tumor evaluation eCRF for non-enhancing lesions (T2/FLAIR)
- Tumor evaluation eCRF for new lesion
- Concomitant medication eCRF for steroid usage
- Clinical status eCRF for ECOG and other clinical evaluation finding
- Overall response eCRF for response category (CR/PR/PD/SD/NA)

14.3.1 Antitumor Effect – Definition

14.3.1.1 Evaluable for toxicity

All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

14.3.1.2 Evaluable for objective response

Only those participants who have measurable disease present at baseline (Cycle 1, Day 1 scan) or post-operatively (group 2) and have received at least one dose of therapy will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of Cycle 1 will also be considered evaluable.)

14.3.1.3 Measurable disease

Bidimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on at least 2 axial slices which are preferably at least 5 mm apart with 0 mm skip. If the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be two times the slice thickness. Measurement of tumor around a cyst or surgical cavity should be considered non measurable unless there is a nodular component measuring ≥ 10 mm in diameter. The cystic or surgical cavity itself should not be measured in determining response. If there are too many measurable lesions to measure at each evaluation, the investigator must measure at least the largest two to be followed before a participant is entered on study, with the total measurement representing the sum of products of the perpendicular diameters. A maximum of five lesions should be measured. The remaining

lesions will be considered non-measureable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

Patients without measurable disease, such as those who undergo a gross total resection, cannot respond and can only achieve stable disease as their best radiographic outcome.

14.3.1.4 Non-measurable evaluable disease

Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1 cm.

14.3.2 Response/Progression Categories

Complete response (CR)

All of the following criteria must be met:

a. Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No new lesions.
c. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d. Participants must be on no steroids or on physiologic replacement doses only.
e. Stable or improved non-enhancing (T2/FLAIR) lesions
f. Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related

Participants with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial response (PR)

All of the following criteria must be met:

a. Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b. No progression of non-measurable disease.
c. No new lesions.
d. All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e. The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.

g. Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

Participants with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Progressive disease (PD)

The following criterion must be met:

a. 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of corticosteroids

and/or one or more of the following:

b. Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids steroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
c. Any new lesion
d. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Easter cooperative Oncology Group (ECOG) performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose.
e. Failure to return for evaluation due to death or deteriorating condition
f. Patients with non measurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a non measurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a 9 × 9 mm lesion [non measurable] increasing to a 10 × 11 mm lesion [measurable]). Ideally, the change should be significant (> 5 mm increase in maximal diameter or ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression.

Note that if there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

Stable disease (SD)

All of the following criteria must be met:

a. Does not qualify for CR, PR, or progression.
b. All measurable and non-measurable sites must be assessed using the same techniques as baseline.
c. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
d. Stable clinically.

Unknown response status

Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

These RANO Response Criteria are also summarized in Table 14-4:

Table 14-4 Summary of the RANO Response Criteria

	CR	PR	SD	PD#
T1-Gd +	None	≥50% decrease	<50% decrease but ≤ 25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA**
Clinical Status	Stable or improve	Stable or improve	Stable or improve	Deterioration*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

*: Progression when this criterion is met **: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

14.3.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

14.3.4 Evaluation of Best response

The best overall response is the best response recorded from the start of the treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started). If a response recorded at one scheduled MRI does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, i.e. still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Participants without measurable disease may only achieve SD or PD as their best "response."

14.3.5 Other Effect Measures

14.3.5.1 Performance Status

Participants will be graded according to ECOG score.

14.3.5.2 Overall survival time

From date of first dose (date of first post-surgery treatment for participants in group 2) to date of death due to any cause.

14.3.5.3 Progression-free survival time

From date of first dose (date of first post-surgery treatment for participants in group 2) to date of progression or death. Participants who stop treatment for causes other than progression may be censored if other therapy is initiated or if regular assessments for assessing progression are no longer available.