Clinical Development

Infigratinib (BGJ398)
Protocol CBGJ398X2204

A phase II multicenter, single arm study of oral BGJ398 in adult patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy

Sponsor	QED Therapeutics, Inc. One Ferry Building, Suite 220 San Francisco, CA 94111
Medical Monitor	PI MD Executive Director, PI QED Therapeutics, Inc. PI
EUDRACT number	2013-005085-19
Development phase	II

Protocol Version Number	Date
00 (original protocol)	21-Feb-2014
01 (Amendment 1)	11-Mar-2015
02 (Amendment 2)	24-Jan-2017
04 (Amendment 3)	19-Sep-2018
05 (Amendment 4)	24-Apr-2019
05.1 (Amendment 4.1; UK-specific)	24-Apr-2019
06 (Amendment 5)	15-Jan-2020

Investigator's Agreement

I have read Protocol CBGJ398X2204 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

_____

Study Site Name

_____

Study Site Number

Signature on this page assures the sponsor that, to the best of the investigator's knowledge, the affiliated Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) operates in accordance with the governing regulations, and that the investigator understands, and agrees to abide by, all governing regulatory obligations and the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and country and regional (local) requirements while conducting this clinical investigation. Additionally, investigator agrees to give access to all relevant data and records to QED Therapeutics monitors, auditors, QED Therapeutics Clinical Quality Assurance representatives, designated agents of QED Therapeutics, IRBs/IECs/REBs, and regulatory authorities as required.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT/SGPT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolutely Neutrophil Count
AST/SGOT	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC_{0-24}	Area Under the Curve 0-24 h
BCRP	Breast Cancer Resistance Protein
BICC1	Bicaudal C homolog 1
BUN	Blood Urea Nitrogen
CI	confidence interval
CL	Clearance
C_{max}	Maximum Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CSF	Colony Stimulating Factor
CSP	Clinical Study Protocol
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic Acid
ECC	Extrahepatic cholangiocarcinoma
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report/Record Form
EOT	End of Treatment
FAS	Full Analysis Set
FGFR	Fibroblast Growth Factor receptor
FGFR1	Fibroblast Growth Factor receptor 1
FGFR2	Fibroblast Growth Factor receptor 2
FGFR3	Fibroblast Growth Factor receptor 3
FLT1	Fms-related tyrosine kinase 1
FMI I	Final Market Image version 1
FMI III	Final Market Image version 3
FMI IV	Final Market Image version 4
GI	Gastrointestinal
hCG	human chorionic gonadotrophin
hERG	Human Ether-à-go-go-Related Gene
IB	Investigator's Brochure
IC_{50}	Half maximal Inhibitory Concentration
ICC	Intrahepatic cholangiocarcinoma
ICF	Informed Consent Form
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
K-M	Kaplan-Meier
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLN	lower limit of normal
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MEK	mitogen-activated protein kinase kinase

MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated acquisition scan
N	Sample size
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OCT	optical coherence tomography
ORR	Overall Response Rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPS	Per protocol set
PR	Partial Response
PT	Prothrombin time
qd	once a day
RNA	Ribonucleic Acid
RP2D	Recommended Phase II dose
RT	Radiation therapy
RT_PCR	Reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TdP	Torsades de Pointes
t_{max}	The time at which the maximum observed concentration (C_{max}) occurs
ULN	Upper Limit of Normal
Vss	Volume of distribution at steady state
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
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 arm 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 noninvestigational 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
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

AMENDMENT 5 (15-JAN-2020)

Amendment rationale

The primary purpose of this amendment is to:

- Revise based on updates to standards for safety and study conduct for BGJ398.
- Add second interim analysis.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough for deletions and underlines for insertions.

- Title page: Updated the Medical Monitor from PI MD, to PI MD; updated protocol version history.
- Investigator's Agreement: Added statement of purpose for signature.
- Synopsis, Purpose and Rationale; Section 1.2.1; Section 2.2: Corrected "pan-FGFR inhibitor" to "FGFR 1-3 inhibitor" (with corresponding data, in Section 1.2.1.1).
- Synopsis, Population; Section 2.2; Section 4.1: Clarified number of patients with and without FGFR2 gene fusions or translocations in Cohort 1.
- Synopsis, Main Inclusion Criteria; Section 5.2 (inclusion criteria 2 and 3); Section 7.1; Section 7.2.4: Clarified requirements for determination of FGFR gene alterations.
- Synopsis, Main Inclusion Criteria; Section 5.2 (inclusion criteria 4 and 5); Sections 14.3.3, 14.3.14, and 14.3.15 (Appendix 3): Removed "or evaluable" from disease criteria.
- Synopsis, Main Exclusion Criteria; Section 5.3 (exclusion criterion 5): Removed "corneal abrasion" as a disqualifying disorder; other edits for consistency.
- Synopsis, Investigational and reference therapy; Section 1.2.1: Defined BGJ398 as "infigratinib," noting other names/codes, for consistency.
- Section 1.2.1.1: Updated BGJ398's effect on kinase activity for consistency with the current Investigator's Brochure.
- Section 1.2.1.2: Replaced outdated clinical safety and efficacy information with a referral to the current Investigator's Brochure.
- Section 1.2.1.2.3 (old)/1.2.1.2.1 (new); Section 6.3.2; Section 14.1 (Appendix 1); Section 14.2 (Appendix 2): Added description of midazolam study, which resulted in

revised QED standards (outlined Section 6.3.2, Section 14.1 [Appendix 1], and Section 14.2 [Appendix 2]).

- Section 2.3; Section 7.1; Section 7.2.3.1; Section 10.5.3: Revised to specify that all patients in Cohorts 2 and 3 (who are treated with FMI IV) will undergo extensive PK sampling, and data will be assessed and compared with data from patients treated with FMI III.

- Section 4.1 (subheading: Survival follow-up), Section 7.1.6 (subheading: Survival follow-up period): Revised to allow survival follow-ups at more frequent intervals.

- Section 4.2: Revised to eliminate obsolete content and to clarify previous data reviews.

- Section 4.2; Section 10: Revised to specify two formal interim analyses planned for Cohort 1. A Sensitivity Analysis Set for Cohort 1 was also defined (Section 10).

- Section 5.3: Removed exclusion criteria 12, 13, and 14.

- Section 5.3: Specified more precise criterion for patients with Gilbert syndrome and specified use of Cockcroft-Gault formula.

- Section 5.3: Exclusion criterion 14 (formerly 17) was made more precise.

- Section 5.3: Exclusion criterion 17 (formerly 20) was revised to cite the Clinical Trials Facilitation Group 2014 guideline and for consistency with other BGJ398 protocols.

- Section 5.3: Added exclusion criterion 20.

- Section 6 and 6.1: Specified “hard gelatin capsules” for BGJ398 oral administration. Updated and clarified instructions for BGJ398 administration.

- Section 6.2.1; Section 6.2.2; Section 6.2.3; Section 6.3.1; Section 6.3.2: Clarified dose modifications and delays, consistent with other BGJ398 protocols, including changes and additions to Table 5 (primarily for serum creatinine, blood bilirubin, hypophosphatemia, and hyperphosphatemia) and management of those and other potential study drug effects (primarily in Section 6.3.1) and of permitted concomitant therapy (Section 6.3.2).

- Section 6.3.3; Section 14.1 (Appendix 1); Section 14.2 (Appendix 2): Removed medications with a known risk of QT/QTc interval prolongation or torsade de pointes from prohibited concomitant therapy (Section 6.3.3 and Appendix 14.2). These medications were included in Table 15, Drugs to be used with caution while on study (Appendix 14.1). This change was made because preliminary PK-QTc analysis of BGJ398 did not show a relationship between drug concentration and QTc prolongation.

- Section 7.1; Section 7.2: Clarified screening and visit windows and in-clinic study drug administration. Added footnote (Table 7) to clarify FGFR2 gene fusion or translocation requirements. Removed provision for replacement of patients in Cohorts 2 and 3 for PK sampling purposes. Clarified molecular pre-screening procedures, as well as imaging requirements and guidelines. Clarified ophthalmic assessments. Added that retinal OCT can images may be collected centrally. Clarified circumstances for study treatment discontinuation. Added detail for extensive PK sampling (Table 11). Added detail for assessment of biomarkers.

- Section 8.1.1: Removed inconsistent sentence regarding AE reporting.

- Section 8.2.2; Section 8.4: Replaced Chiltern Drug Safety with Covance Safety. Replaced the email address GlobalSAEInbox@chiltern.com with the email address SAEintake@covance.com.

- Section 8.4: Clarified follow-up for pregnancy.

- Section 9.1: Updated data confidentiality.

- Section 9.4: Updated database management and quality control.

- Section 11.3: Clarified informed consent procedures.

- Section 11.7: Updated confidentiality of study documents and patient records.

- Section 13: Updated reference list.

- Section 14.3.16 (Appendix 3); Section 14.4 (Appendix 4): Moved references to Section 13.

- Section 14.5 (Appendix 5): Added list of highly effective methods of contraception excerpted from the Clinical Trials Facilitation Group 2014.

- Throughout: Removed “et al” from citations in text, according to updated QED standards, and other administrative or editorial changes.

IRBs/IECs

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. Study centers are required to update and submit for approval a revised informed consent that takes into account the changes described in this protocol amendment.

AMENDMENT 4 (24-APR-2019)

Amendment rationale

The primary purpose of this amendment is to:

- Revise assessment of overall response for the primary endpoint for patients with FGFR2 gene fusions or translocations from confirmation by investigator to confirmation by independent central confirmation (according to FDA advice), and change investigator assessment of overall response from a primary to a secondary objective.

- Include an interim analysis, occurring when the patients enrolled prior to amendment 2 have potentially been followed up for at least 10 months after their initial exposure to study treatment.

- Revise the RECIST criteria guidelines (Appendix 3, Section 14.3) to be consistent with published criteria.

- Include 2 additional cohorts, allowing enrollment of patients with known FGFR1, 2, or 3 activating mutation or FGFR1 or 3 fusions or translocations (Cohort 2; 20 patients) and patients with FGFR2 gene fusions or translocations after previous treatment with gemcitabine-containing regimen followed by progression on an FGFR inhibitor (excluding BGJ398) (Cohort 3; 10 or 20 patients). Rationale is provided in Section 2.2.

- Include an interim analysis for Cohort 3 when the first 10 patients who receive study treatment have the potential to complete their second scheduled scan; this analysis is to determine if an additional 10 patients will be added to the cohort.

- Clarify that 108 patients with FGFR2 gene fusions or translocations will be included in Cohort 1, and this sample size is the basis of statistical analyses for this group.

- Allow another formulation of BGJ398 (ie, final market image version 4, or FMI IV) to be administered to patients, with accompanying pharmacokinetic analysis and analysis comparing the 3 formulations administered in the study.

- Extend follow-up for survival from one year to 5 years after discontinuation of study treatment or until patients have died, withdrawn consent, or been lost to follow-up.

- Exclude patients with history and/or current evidence of extensive tissue calcification of the vascular system (according to FDA advice).

- Modify criteria for interruption and re-initiation of BGJ398 treatment (Table 5) in accordance with QTc evaluation plan submitted to FDA and for consistency with other ongoing studies of BGJ398.

- Include retinal optical coherence tomography (OCT) in the ophthalmic examination.
- Revise PK sparse sampling times.
- Add section describing adverse event reporting for overdose of BGJ398 and for Hy's Law criteria.
- Add statement that any suspected transmission of an infectious agent via a medicinal product will be considered an SAE at study centers in the EU.
- Revise and update list of drugs to be used with caution on study (Table 15) and list of prohibited medication while on study (Table 16).
- Add FGFR1/2/3 known activating mutations list for Cohort 2 inclusion criteria (Appendix 4, Section 14.4.).
- Change the Medical Monitor from PI MD, MSCE, to PI MD.
- Revert to original protocol version numbering (ie, undo the version numbering that was reassigned for versions 00, 01, and 02 in amendment 3); consequently, no version 03 exists for this protocol, and protocol version numbering now corresponds with protocols distributed for study conduct.
- Revise administrative details and edits for consistency and clarity throughout the protocol, notably including (1) collapse of Section 8.3.1 (now deleted) into Section 8.1.1 to eliminate redundancy and inconsistency and (2) revision of nomenclature from "FMIv3" to "FMI III" for consistency within the BGJ398 development program.

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 underline for insertions.

- Title page: Changed the Medical Monitor name and contact information. Changed the protocol version numbering.
- Clinical Protocol Approval Page: Removed from protocol and replaced by separate approval page (not included within the protocol).
- Protocol Summary: Revised to account for amendment changes in the main body.
- Section 1.2.1.2.3: Clinical pharmacokinetics: Revised T_{max} from 2 hours to 3-4 hours.
- Section 2.2, Rationale for the study design: Added description for all cohorts, with rationale for Cohorts 2 and 3.
- Section 2.3, Rationale for dose and regimen selection: Added description and rationale for the FMI IV formulation of BGJ398.

- Section 3, Objectives and endpoints: Clarified objectives for Cohort 1 and the overall study. Added objectives and endpoints for Cohorts 2 and 3.

- Section 4, Study design: Described new cohorts and revised total number of patients to be enrolled in the study. Added description of interim analyses. Added footnote about screening assessments to Figure 1. Changed survival follow-up period from 1 year to 5 years. Described interim analyses planned. Clarified the definition of end of the study.

- Section 5, Population: Added entry criteria specific to Cohorts 2 and 3. Added "vascular system" to exclusion criterion #6. Added exclusion criterion #22 for all cohorts.

- Section 6, Treatment: Added FMI IV formulation. Clarified dosing instructions. Changed dosing window from 24±2 hours to 24±4 hours. Described the timing of FMI IV administration. Added that proton pump inhibitors should be avoided. Revised criteria for interruption and re-initiation of BGJ398 treatment to be consistent with other ongoing studies. Clarified prohibited concomitant therapy for "other investigational and antineoplastic therapies." Added description of FMI III and FMI IV drug supply.

- Section 7, Visit Schedule and Assessments: Added footnotes to Table 7 to clarify assessments. Changed screening period from -28 days to -21 days and added footnote to Table 7 to clarify. Added a Day 15 visit for Cycles 4-6 to accommodate new PK sampling times. Clarified that no further imaging is required for patients who have documented radiographic disease progression and continue study treatment. Clarified molecular pre-screening for the cohorts. Added OCT as an ophthalmic assessment. Added 4-hour post-dose ECG assessment on Cycle 1 Days 1 and 15, and clarified recording of ECGs and cardiac imaging assessments. Defined PK sampling by cohort. Added sparse PK sampling times for newly enrolled patients at 4 hours post-dose on Cycle 1 Days 1 and 15; and added PK sampling pre-dose and 4 hours post-dose on Day 15 of Cycles 2-6 (Table 10). Added explanation of future research and storing of biological samples for such research in cholangiocarcinoma.

- Section 8, Safety Monitoring and Reporting: Revised to eliminate redundancy and inconsistency among Sections 8.1.1, 8.1.2, and 8.1.3. Removed Section 8.1.3. Added subsections to describe reporting overdose of BGJ398 and Hy's Law potential AEs. Clarified reporting of pregnancy and follow-up.

- Section 10, Statistical Methods and Data Analysis: Revised to account for analyses of new cohorts. Refined definitions of analysis sets and clarified and updated all analyses based on the new cohorts and definitions. Overall response rate (ORR) analysis was updated from Bayesian to Frequentist approach; the ORR will be estimated with exact binomial 95% confidence interval (CI). Revised sample size calculations based on new cohorts and analysis groups. Revised plans for interim analyses.

- Section 13, References (Available upon Request): Added 3 new references.
- Section 14, Appendices: Appendix 1: Revised list of drugs to be used with caution.
- Section 14, Appendices: Appendix 2: Revised list of prohibited medication.
- Section 14, Appendices: Appendix 3: Revised RECIST criteria guidelines to be consistent with published criteria and simplified to consolidate details and move them to more relevant sections (ie, Section 10).
- Section 14, Appendices: Appendix 4: Added appendix to list FGFR1/2/3 allowed mutations for qualification for study entry.

IRBs/IECs

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. Study centers are required to update and submit for approval a revised informed consent that takes into account the changes described in this protocol amendment.

AMENDMENT 3 (19-SEP-2018)

Amendment Rationale

The main purpose of this amendment is to change the Sponsor name from Novartis to QED Therapeutics and provide safety reporting information for the clinical research organization working with QED Therapeutics.

Changes to the protocol

1. Administrative updates are made throughout the protocol to change Sponsor from "Novartis" to "QED Therapeutics".

2. Title Page was changed to remove Protocol Authors and replace with Medical Monitor; Sponsor name was also added. Added logo for QED.

3. Added dates for each protocol amendment to the Title Page of the protocol.

4. Added an Investigator's Signature page.

5. List of Abbreviations was updated to remove abbreviations not used in the protocol.

6. Section 2.3.

   Changed From:

   Patients enrolled in this study will receive 125 mg qd of BGJ398 on a 3 weeks on (21 day) /1 week off (7 day) schedule. This dose level and regimen is based on experiences from the CBGJ398X2101 trial.

   Changed To:

   Patients enrolled in this study will receive 125 mg qd of BGJ398 on a 3 week~~s~~ on (21 day) /1 week off (7 day) schedule <u>in 28-day cycles</u>. This dose level and regimen is based on experiences from the CBGJ398X2101 trial.

7. Section 6.1.3

   Changed From:

   All patients will receive BGJ398 daily on a three week on (21 days), one week off (7 days) schedule in 28-day cycles. Patients may continue treatment with BGJ398 until the patient experiences unacceptable toxicity, disease progression, and/or treatment is discontinued at the discretion of investigator or withdrawal of consent.

   Changed To:

   All patients will receive BGJ398 daily on a three week on (21 days), one week off (7 days) schedule in 28-day cycles. Patients may continue treatment with BGJ398 until

the patient experiences unacceptable toxicity, disease progression, ~~and/or~~ treatment is discontinued at the discretion of investigator or withdrawal of consent, or death.

8. Section 6.5.3.2

   Changed From:

   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.~~

   Changed To:

   At study close-out, and, as appropriate during the course of the study, the investigator will provide access to all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the monitor.

9. Section 6.5.4

   Changed From:

   The study drug ~~supply~~ can be destroyed at the ~~local Novartis facility, Drug Supply group or third party, as appropriate. Drug supply can be destroyed at the~~ site if permitted by local regulations.

   Changed To:

   The study drug can be destroyed at the site if permitted by local regulations. Alternatively, the study drug can be destroyed at a third party depot.

10. Section 7.1 (Table 5: Visit Evaluation Schedule): Removed reference to Section 7.1.5 of the protocol on the row for Tumor Response per RECIST 1.1 (the section reference was incorrect) and changed the reference on the row for Survival Follow-up from Section 7.1.5 to 7.1.6. Also removed footnote a, is it did not seem to be relevant.

11. Section 7.2.3.1: Added the missing volume (3mL) to the PK sampling table for the 2 hour postdose assessment at Cycle 1 Day 2.

12. Section 7.2.4.1 and 7.2.4.2: Removed reference to the Sponsor's laboratory manual in the following sentence.

    The sample collection must be captured on the appropriate eCRF and requisition page(s). Detailed instructions for the collection, handling, labeling, and shipment of samples are outlined in the CRO Laboratory Manuals ~~or Novartis lab manual~~.

13. Section 8.2.2.

Changed From:

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…...

….. 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 submit the completed form within 24 hours to ~~Novartis~~. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.
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, a ~~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.

Changed To:

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 Chiltern Drug Safety (email: GlobalSAEInbox@chiltern.com; FAX: 1-888-726-8416) within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 days period should only be reported to Chiltern Drug Safety if the investigator suspects a causal relationship to the study treatment…...

….. 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 submit the completed form within 24 hours to Chiltern Drug Safety (email: GlobalSAEInbox@chiltern.com; FAX: 1-888-726-8416). Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.
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 study treatment, a Chiltern Drug Safety associate may urgently require further information from the investigator for Health Authority reporting. Chiltern Drug Safety 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.

14. Section 8.4

Changed From: 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.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to ~~the oncology Novartis~~ Drug Safety ~~and Epidemiology (DS&E) department~~.

Changed To: To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Chiltern Drug Safety (email: GlobalSAEInbox@chiltern.com; FAX: 1-888-726-8416) within 24 hours of learning of its occurrence.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to Chiltern Drug Safety (email: GlobalSAEInbox@chiltern.com; FAX: 1-888-726-8416).

15. Section 10.6.1.1

Changed From: ~~As the project standard,~~ PD markers collected in the clinical database will be analyzed by ~~Novartis Oncology BDM.~~

Changed To: PD markers collected in the clinical database will be analyzed by QED Therapeutics or designated CRO.

16. Section 11.5

Changed From: In addition, results of interventional clinical trials ~~in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion~~.

……~~For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.~~

Changed To: In addition, results of interventional clinical trials will be posted publically per local regulations.

17. Section 14.3 (Appendix 3): Removed the row for Document Type.

~~Document type:~~	~~TA Specific Guideline~~
Document status:	Version 3.1: 29-Nov-2011 Version 3.0: 19-Oct-2009 Version 2.0: 18-Jan-2007 Version 1.0: 13-Dec-2002

18. Section 14.3.1 (Appendix 3)

    Changed From:

    The efficacy assessments described in Section 14.3.2 and the definition of best response in Section 14.3.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. ~~Section 14.3.18 is summarizing the "time to event" variables and rules~~ which ~~are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria, do not define these variables in detail. Section 14.3.28~~ of this guideline describes data handling and programming rules. ~~This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.~~

    Changed To:

    The efficacy assessments described in Section 14.3.2 and the definition of best response in Section 14.3.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.3.27 of this guideline describes data handling and programming rules.

19. Section 14.3.18 (Appendix 3)

    Changed From:

    ~~14.3.18 Time to event variables~~

    Changed To:

    [no text- there was nothing but a header for this section of the appendix; all subsequent sections were renumbered accordingly]

20. Minor editing and formatting changes were made. Due to errors in the protocol file received from Novartis, the Table of Contents and Lists of Tables and Figures were regenerated. In doing so, the figures and tables were renumbered, as follows:

OLD FIGURE NUMBER	NEW FIGURE NUMBER
Figure 4-1	Figure 1
OLD TABLE NUMBER	**NEW TABLE NUMBER**
Table 3-1	Table 1
Table 6-1	Table 2
Table 6-2	Table 3
Table 6-3	Table 4
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Table 14-5	Table 19
Table 14-6	Table 20
Table 14-7	Table 21

IRBs/IECs

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 2 (24-JAN-2017)

Amendment rationale

The primary purpose of this amendment is to:

1. Increase enrollment to approximately 120 patients in order to 1) introduce a new drug formulation, Final market image version 3 (FMIv3) and 2) allow further evaluation of the safety and preliminary efficacy signal observed in the first 61 patients enrolled. Enrollment will be restricted to those patients with intrahepatic cholangiocarcinoma whose tumors have FGFR2 gene fusions/translocations; patients with other FGFR genetic alterations will not be enrolled. The increased sample size will permit more precise estimation of response rate, duration of response and progression free survival.

   Of the 61 patients enrolled to the BGJ398X2204 study (30-Jun-2016), there were 58 patients evaluable for preliminary assessment of efficacy (with valid baseline and at least one valid post-baseline assessment). In these 58 patients, the investigator-assessed ORR (confirmed responses only) is 15.5%. Disease control rate is 79.3% (46 patients). Additionally, out of the 37 patients who achieved stable disease, 6 patients achieved PR in one scan (did not have subsequent scan confirming the PR). Of the 61 patients, 39 (63.9%) had a PFS event (3 deaths and 36 patients progressed as per RECIST). The median PFS is estimated at 175 days (95% CI: 130 – 230 days).

   Final Market Image version 3 (FMIv3) will replace the current drug formulation (FMIv1) in the current study for all patients enrolled following the implementation of this protocol amendment. These two formulations have been previously compared in two separate studies [CBGJ398X2103 and CBGJ398X2106] to the clinical service form which was used to establish MTD of BGJ398 at 125 mg qd [CBGJ398X2101]. Cross-study comparison of the exposures (AUC and C_{max}) between FMIv3 and FMIv1 indicated that exposure of BGJ398 from the FMIv3 formulation is about 21-35% higher than that of FMIv1 (21% for AUC_{inf}, 29% for C_{max} and 35% for AUC_{last}). Although BGJ398 has demonstrated high interpatient variability in exposure at the 125 mg dose, on average, steady-state concentrations provide target coverage over the dosing interval at doses associated with efficacy. As observed events with BGJ398 are readily monitorable and considered manageable, patient's doses can be individually titrated to maximize therapeutic potential and minimize toxicity across a wide exposure range. Thus, the dose of FMIv3 125 mg qd should pose no additional safety concerns. However, pharmacokinetics, safety and tolerability data from the first 20 patients treated with FMIv3 up to the end of cycle 1 of treatment will be assessed and compared with the historical data from patients treated with FMIv1. Serial blood samples will also be collected from the remaining patients in this study to further characterize the pharmacokinetic properties of FMIv3 in this patient population.

2. In order to allow for independent confirmation of the response rate, duration of response, and progression-free survival results, initiate independent review of radiologic assessments by an imaging CRO designated by Novartis.

3. Update biomarker strategy:

    a. Add cell free DNA (cf DNA) sampling to explore correlation between genetic alterations in tumor tissue at baseline, clinical response and development of resistance

    b. Discontinue CA19-9 sample collection as the test is not used across the majority of sites for disease assessment

    c. Discontinue whole blood collection for exploratory germline analysis as this will no longer be analyzed

    d. Remove language pertaining to the Novartis optional companion sample collection protocol as it is no longer applicable for this protocol.

4. Reduce frequency of cardiac imaging at cycle 3 and cycle 4 as there is no cardiac risk observed with BGJ398

5. Pregnancy and contraception language have been updated

6. Correct typographical errors and inconsistencies throughout the document.

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 underline for insertions.

- Protocol summary: Updated to reflect changes based on the amendment Section 1.2.1.2.1 Clinical safety: Added safety data available to date.

- Section 1.2.1.2.2 Clinical efficacy: Added efficacy data available to date.

- Section 1.2.1.2.3 Clinical pharmacokinetics: Updated to reflect current understanding of pharmacokinetic data

- Section 2.3 Rationale for dose and regimen selection: Updated to include FMIv3

- Section 3 objectives and related endpoints: Added objective related to PK of FMIv3

- Section 3 objectives and related endpoints: Added exploratory analysis of circulating tumor DNA, removed CA19-9 biomarker analysis as it is not commonly available at participating centers

- Section 4.1- Study design: Total patients to be enrolled has been updated to "approximately 120"

- Section 4.3- Assessment of potential mechanism of resistance: Removed reference to optional companion sample collection as this is no longer applicable for the study

- Section 5.1- Updated to restrict enrollment to FGFR2 fusion/translocations

- Section 5.2- Inclusion criteria: Removed reference to other FGFR genetic alterations. As of this amendment, patients with only FGFR2 fusion/translocations will be enrolled.

- Section 5.3: Updated exclusion criteria regarding pregnancy contraception requirements. Requirement for use of contraception after the last dose of BGJ398 remains unchanged.

- Section 6.1- Study treatment: Added language regarding introduction of FMIv3

- Section 6.3 Concomitant medications: Added clarification for use of concomitant medications that are listed in both Appendix 1 (List of concomitant medications) and Appendix 2 (List of prohibited medications).

- Section 7.1.2- Screening: removed language regarding screening window to make it consistent with other sections

- Section 7.1, Table 7-1 Visit evaluation schedule: Added blood collection for exploratory biomarker- circulating tumor DNA analysis

- Section 7.1, Table 7-1 Visit evaluation schedule: Removed germline whole blood collection as the exploratory analysis will not be performed

- Section 7.1, Table 7-1 Visit evaluation schedule: Removed CA19-9 assessment as test is not routinely available at all participating centers

- Section 7.1. Table 7-1 Visit evaluation schedule: Removed cardiac imaging requirement at cycle 3 and cycle 4 as there is no known cardiac risk noted based on available data

- Section 7.1. Table 7-1 Visit evaluation schedule: Removed footnote "c" related to companion sample collection

- Section 7.1.4 Discontinuation of study treatment: revised language regarding study treatment discontinuation

- Section 7.1.5 Withdrawal of consent: new section added for withdrawal of consent

- Section 7.1.7 Lost to follow-up: New section regarding those patients lost to follow-up

- Section 7.2.1- Efficacy: Added information related to tumor evaluation by independent review

- Section 7.2.3- Pharmacokinetics: Added information related to PK analysis

- Section 7.2.4.3- Exploratory biomarkers: Removed whole blood germline analysis sampling

- Section 7.2.4.4- Exploratory biomarkers: Added section on blood sampling for circulating
  DNA

- Section 7.2.4.5- CA19-9 assessment: removed the section as this is no longer being collected for this study

- Table 7-4- Pharmacokinetic blood collection time points for patients: updated the title to add sparse PK sampling requirement

- Table 7-5 - Pharmacokinetic blood collection time points for patients: added new table for collection of extensive PK samples for first 20 patients treated with FMIv3

- Table 7-6- Biomarker sample collection plan: updated to remove germline blood sample and added blood sample for cell free DNA analysis

- Section 8.1.3.1- Safety: Updated the reporting language for SAEs

- Section 9.4- Database management and quality control: removed language regarding companion sample collection

- Section 10- Statistical method and data analysis: Updated to reflect the data analysis in terms of formulation change

- Section 11.5- Publication of study protocol and results: New section regarding Novartis' publication policy

IRBs/IECs

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AMENDMENT 1 (11-MAR-2015)

Amendment rationale

The purpose of this amendment is as follows:

- Inclusion/Exclusion criteria were modified to clarify patient eligibility and align with standard of care treatment practice for cholangiocarcinoma.

- 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 phosphorous 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.

- Evaluations of cardiac function by echocardiogram/MUGA scan were added on day 1 of cycles 2, 3 and 4 to monitor changes in left ventricular ejection fraction (LVEF) and make monitoring frequency consistent across BGJ398 protocols. Asymptomatic and reversible decreases in LVEF have been noted in patients treated with BGJ398.

- The emergence of acquired resistance to therapy is a major problem for patients with cancer. Under this amendment, language has been inserted to allow the collection of tumor tissue at baseline and upon the development of acquired resistance to treatment as described in the optional companion sample collection protocol. The purpose of these samples and a sample of normal tissue to aid in the identification of somatic variants in the tumor is to identify genetic changes in the tumor that may underlie treatment resistance. Two blood samples are also collected to test the potential value of circulating cell free tumor DNA as a possible replacement in some circumstances for tumor biopsies.

- Minor inconsistencies, edits, and typographical errors that were identified after the finalization of the original protocol have been corrected with this amendment.

Changes to the protocol

- Updated Protocol Summary to further clarify inclusion criteria regarding patient eligibility coming off a prior regimen due to toxicity

- Updated Section 1.2.1.2.1, clinical safety

- Updated Section 1.2.1.2.2, clinical efficacy

- Updated Section 4.3 with wording regarding the Novartis companion sample collection protocol to study the mechanism of drug treatment resistance

- Updated Section 5.1 to further clarify Inclusion criteria regarding patient eligibility coming off a prior regimen due to toxicity

- Updated Section 5.2, inclusion criteria #1 to add that patients with cancers of the gallbladder and ampulla of Vater are not eligible and inclusion criteria #5 to further clarify patient eligibility

- Updated Section 5.3, exclusion criteria #1 to add that patients are ineligible if they had prior treatment with a MEK or selective FGFR inhibitor, #16, clarified the creatinine/creatinine clearance criteria, #8 removed "History and/or, #11 and Section 6.1.1.1 for consistency on which fruits are prohibited, #17 to allow for corrected total calcium, #18 to read 470 msec.

- Updated Section 6.1.1.1 to clarify administration of BGJ398

- Updated the lipase/amylase elevation information, hyperphosphatemia management and creatinine clearance information in Table 6-3

- Removed Table 6-4 as the information was duplicative and the information can be found in Table 6-3

- Revised Section 6.3, Concomitant medications

- Revised Section 6.3.2, QT/QTc interval prolongation or torsade de pointes medications

- Revised Section 6.3.3, Prohibited concomitant therapy to include information on known risk of QT/QTc interval prolongation or torsades de pointes medications

- Removed RSTANCE2101 language from Section 7.1 to be replaced in Section 9 (Data Collection and Management)

- Updated Table 7-1 to include clarifications regarding the Novartis companion sample collection protocol information

- Updated Table 7-3 to allow for corrected total calcium

- Updated Section 7.2.2.7 to clarify time frame intervals for cardiac assessments.

- Updated Section 8.2.2 to include SAE information regarding the Novartis companion sample collection protocol

- Updated Section 9.4 to include the language required for the Novartis sample collection protocol regarding data management

- Revised Appendix 1, Table 14-1

- Revised Appendix 2, Table 14-2

- Minor inconsistencies, edits and typographical errors that were identified after the finalization of the original protocol have been corrected with this amendment.

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

IRBs/IECs

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PROTOCOL SUMMARY

Protocol number	CBGJ398X2204
Title	A phase II multicenter, single arm study of oral BGJ398 in adult patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy
Brief title	A single arm study of oral BGJ398 in adult patients with advanced or metastatic cholangiocarcinoma
Sponsor and Clinical Phase	QED Therapeutics, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the efficacy of the targeted, selective FGFR 1-3 inhibitor BGJ398 when administered as a single agent to patients with genetically selected advanced or metastatic cholangiocarcinoma through estimation of the overall response rate. Molecular characterization of these tumors at baseline and at the time of progression may allow for increased understanding of potential treatment combinations, as well as primary and acquired resistance mechanisms.
Primary Objective (Cohort 1)	To evaluate the efficacy of single agent BGJ398 in patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations or other FGFR genetic alterations as measured by overall response assessed by central imaging review according to RECIST v1.1.
Secondary Objectives (Cohort 1 and Overall Study)	Cohort 1: To further evaluate the efficacy of single agent BGJ398 as measured by overall response assessed by investigator; progression free survival, best overall response, disease control assessed by investigator and by central imaging review as per RECIST 1.1; and overall survival. Cohort 1: To characterize the safety and tolerability of single agent BGJ398 by type, frequency, and severity of AEs and SAEs. Overall study: To determine selected trough and 2-hr or 4-hr plasma concentrations of BGJ398 and its metabolites. Overall study: To characterize the pharmacokinetic profile of BGJ398 FMI III and FMI IV formulations.
Study design	This is a multi-center, open label, single arm phase II study evaluating BGJ398 anti-tumor activity in advanced or metastatic cholangiocarcinoma patients with FGFR genetic alterations. Oral, monotherapy BGJ398 will be administered once daily for the first 3 weeks (21 days) of each 28-day cycle. Treatment period will begin on Cycle 1 Day 1 and will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, or death. Patients will be evaluated for tumor response radiographically every 8 weeks until disease progression or discontinuation from study using RECIST 1.1 criteria.
Population	Adult patients with histologically or cytologically confirmed advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations or other FGFR genetic alteration who have evidence of radiologic progression following a cisplatin-and gemcitabine-containing regimen for advanced disease or a gemcitabine-containing regimen for those who are considered intolerant to cisplatin will be enrolled. Up to approximately 160 adult patients over age 18, both male and female will be enrolled. Three cohorts of patients comprise the study population:

	• Cohort 1: ~120 patients, ~106 with FGFR2 gene fusions or translocations and 14 with other FGFR genetic alterations enrolled under the original protocol and amendment 1. • Cohort 2: ~20 patients with FGFR genetic alterations other than FGFR2 gene fusions or translocations. • Cohort 3: Up to ~20 patients with FGFR2 gene fusions or translocations who have received a prior FGFR inhibitor. Objectives for Cohorts 2 and 3 are exploratory.
Main Inclusion criteria	• Patients with histologically or cytologically confirmed cholangiocarcinoma at the time of diagnosis. Patients with cancers of the gallbladder or ampulla of Vater are not eligible. • Written documentation of local laboratory or central laboratory determination of the following FGFR gene alterations from a sample collected before BGJ398 treatment: ○ Cohort 1: FGFR2 gene fusions or translocations. ○ Cohort 2: one of the following: (a) FGFR1 fusions or translocations, (b) FGFR3 fusions or translocations, or (c) FGFR1/2/3 mutation known to be an activating mutation and noted in Appendix 4. ○ Cohort 3: FGFR2 gene fusions or translocations. • Patients must have received at least one prior regimen containing gemcitabine with or without cisplatin for advanced or metastatic disease. Patients should have had evidence of progressive disease following prior regimen, or if prior treatment discontinued due to toxicity must have continued evidence of measurable disease • ECOG performance status ≤ 1 (Patients with ECOG performance status of 2 may be considered on a case-by-case basis after discussion with QED Therapeutics). • Cohort 3 only: Documented prior treatment with FGFR inhibitor other than BGJ398/infigratinib.
Main Exclusion criteria	• Prior or current treatment with a mitogen-activated protein kinase (MEK) inhibitor (all cohorts), BGJ398/infigratinib (all cohorts), or selective FGFR inhibitor (Cohorts 1 and 2 only). • Current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, inflammation or ulceration, keratoconjunctivitis, confirmed by ophthalmic examination • History and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium, vascular system, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification • Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BGJ398 (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection) • Current evidence of endocrine alterations of calcium/phosphate homeostasis, eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis etc. • Concurrently receiving or planning to receive during participation in this study, treatment with agents that are known strong inhibitors or inducers of CYP3A4. Medications which increase serum phosphorus and/or calcium concentration are excluded (Refer to Appendix 2 for list of prohibited medications). Patients are not permitted to receive enzyme-inducing anti-epileptic drugs.

	• Cohort 3 only: Known existence of a V564F mutation in the FGFR2 gene.
Investigational and reference therapy	Infigratinib (also known as BGJ398, BBP-831, and infigratinib phosphate) administered as monotherapy
Efficacy assessments	Tumor response according to RECIST Version 1.1, and survival
Safety assessments	Adverse event (AE) reporting and changes from baseline in laboratory parameters, vital signs, ophthalmic assessment, cardiac imaging
Other assessments	Pharmacokinetic assessment: Blood samples will be collected for the measurement of the plasma concentrations of BGJ398 and its metabolites. Biomarker assessment: Archival or newly obtained tumor samples will be collected to explore mechanisms of resistance to cancer treatment through analysis of next generation DNA sequencing data from tumor samples at baseline and after the development of disease progression (whenever available). Blood samples will be collected at screening and throughout the study for cell free DNA analysis to explore correlation with genetic alterations in tumor tissue at baseline, clinical response and development of resistance
Data analysis	Data will be analyzed by QED Therapeutics and/or designated CRO. 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 and all relevant PK and PD measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.
Key words	BGJ398, cholangiocarcinoma, FGFR2 gene fusions or translocations, FGFR genetic alterations, platinum-containing regimen, molecular pre-screening, RECIST 1.1

1 BACKGROUND

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Cholangiocarcinoma is a rare, heterogeneous malignancy which originates from the neoplastic transformation of cholangiocytes into intrahepatic, perihilar, or distal extrahepatic tumors (Alpini 2001). In the United States, approximately 3,000 patients are diagnosed with cholangiocarcinoma of both the intra- and extrahepatic biliary system annually. Cholangiocarcinoma is more prevalent in Asia and Middle East, mostly because of a common parasitic infection of the bile duct (American Cancer Society 2012). Men are slightly more likely to develop cholangiocarcinoma, while incidence increases with age in both sexes (Patel 2002).

Usually, cholangiocarcinomas are adenocarcinomas and have poor prognosis with limited treatment alternatives. This is partly due to the late onset of symptoms and relative resistance to the therapies currently available. Moreover, conventional chemotherapy and radiation therapy (RT) have not been shown to be effective in prolonging long-term survival. Photodynamic therapy combined with stenting has been reported to be effective as a palliative treatment; however, it is not curative (Sirica 2005). In April 2010, the ABC-02 trial was published, which was the first phase III randomized, controlled trial in this patient population where patients were randomly assigned to receive cisplatin plus gemcitabine or gemcitabine alone (Valle 2010). In this study, the combination of gemcitabine/cisplatin demonstrated improved progression-free survival (PFS) and overall survival (OS) compared to gemcitabine alone. The median overall survival was 11.7 months in the cisplatin–gemcitabine group and 8.1 months in the gemcitabine group. The median progression-free survival was 8.0 months in the cisplatin–gemcitabine group and 5.0 months in the gemcitabine-only group. Still, cholangiocarcinoma patients relapsing after first line therapy have few therapeutic options, and there is no established second line standard of care. Response rates to currently available therapy are in the single digits.

The most recent guidelines regarding treatment of advanced biliary tract cancers, developed by the National Comprehensive Cancer Network (NCCN), recommend the use of gemcitabine, capecitabine, or 5-fluorouracil (5-FU), either as single agents or in combination with a platinum analog (oxaliplatin or cisplatin), or the combination of gemcitabine and capecitabine, with the combination of gemcitabine and cisplatin receiving a category 1 recommendation. None of these agents are FDA approved primarily for use in biliary tract cancers. Moreover, multi-agent chemotherapeutic approaches do not confer a durable benefit in patients with metastatic and/or relapsed disease, and fewer than 5% of patients survive 5 years after diagnosis of advanced disease. Thus, there is a real need to develop novel therapeutic strategies for cholangiocarcinoma based on exploiting select molecular targets that would significantly impact clinical outcomes. Molecular alterations implicated in the dysregulation of cholangiocarcinoma cell growth and survival, aberrant gene expression, and invasion and metastasis have been considered potential therapeutic targets (Sirica 2005).

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

1.2.1 Overview of BGJ398

BGJ398 (infigratinib; also known as BBP-831 and infigratinib phosphate) is an orally bio-available, potent and selective and ATP-competitive inhibitor of fibroblast growth factor receptors (FGFRs) 1-3, 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-ethylpiperazin-1-yl)phenylamino]-pyrimidin-4-yl}-1-methylurea phosphate (1:1).

Please refer to the current Investigator's Brochure for the most recent information on BGJ398.

1.2.1.1 Nonclinical experience

At the cellular level, BGJ398 selectively inhibits the kinase activity of FGFR1, FGFR2, FGFR3, as measured by inhibition of receptor autophosphorylation with IC_{50} values of 4 - 5 nM for FGFR1, FGFR2 and FGFR3. Infigratinib is less potent in inhibiting FGFR4, with an IC_{50} of 164 nM for FGFR4.

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 2011). In line with its cellular activity, BGJ398 shows anti-tumor activity in multiple models bearing FGFR genetic alterations (Guagnano 2012; Konecny 2013).

1.2.1.1.1 Animal drug metabolism and pharmacokinetics

In all species tested, BGJ398 exhibited a high plasma CL (clearance) and a large Vss (Volume of distribution at steady state). 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. In addition, *in vitro* data indicate that BGJ398 is primarily a CYP3A4 substrate.

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 KI=37.3 μM and Kinact=0.0547 min -1. In addition, CQM157, a recently identified metabolite in circulating plasma from patients, is also shown to be 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 (IC_{50} less than 5 μM).

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 bilateral opacity with dose-dependent incidence, as assessed by in vivo ophthalmology. The clinical/ophthalmoscopic finding was associated with reversible, diffuse epithelial keratopathy at the highest dose of 10 mg/kg. In the 2-week rat toxicity study, doses of 20 mg/kg/day did lead to vasculopathy associated with moribundity after 6 administrations.

In dog toxicity study, minimal, fully reversible retention of the primary spongiosa and minimal increase in mineralization in lung and kidney without observed functional impairment were observed.

1.2.1.2 Clinical experience

Please refer to the current Investigator's Brochure for the most recent clinical safety and efficacy information on BGJ398.

1.2.1.2.1 Clinical pharmacokinetics

The pharmacokinetics (PK) of BGJ398 and active metabolites have been evaluated following single and repeat daily doses in the ongoing phase I study (CBGJ398X2101). At 5 and 10 mg/day, plasma concentrations were low and frequently below the lower limit of quantification. Plasma concentrations were consistently quantifiable starting at 20 mg/day.

Following a single dose, median T_{max} was approximately 3-4 hours. The mean AUC_{0-24} on Day 1 increased approximately 9 fold from 20 to 150 mg. The mean terminal elimination half-life on Day 1($T_{1/2}$) was 3-7 hr. Despite the relatively short half-life on Day 1, accumulation was observed with daily dosing at doses ≥ 60 mg, likely due to auto-inhibition of CYP3A4 mediated clearance pathways. Mean accumulation ratio (R_{acc}) ranged from 3 to 8 on Days 15 and 28. Since dose interruptions occurred frequently following continuous daily dosing of BGJ398, PK parameters on Day 28 should be viewed with caution. The interpatient variability was high for BGJ398.

Concentration data from active metabolites BHS697 (desethyl metabolite) and BQR917 (Noxide) was available across all cohorts. CQM157 (aniline metabolite) was analyzed in a few patients following Amendment 6 of the BGJ398X2101 clinical protocol. In most patients, BHS697 and BQR917 were measurable at levels of ~5-50%, and <15% of parent exposure, respectively. Mean exposures on Day 1 (N=8) for CQM157 relative to BGJ398 varied across patients (3% -300%). CQM157 (N=4) did not appear to accumulate on daily dosing, whereas accumulation was observed for BGJ398 and metabolites BHS697 and BQR917.

In vitro studies indicated that infigratinib inhibits CYP3A4; therefore, a clinical drug-drug interaction study (QBGJ389-106) was conducted to assess the effects of multiple doses of infigratinib on midazolam (a sensitive CYP3A4 substrate). Midazolam exposure in terms of AUC_{inf} and C_{max} was minimally reduced (11% and 1%, respectively). For the active metabolite, 1-hydroxymidazolam, exposure increased by 19% and 26% for AUC_{inf} and C_{max}, respectively. Overall, these results indicate that infigratinib had a small effect on the metabolism of midazolam and can be considered a weak CYP3A4 inhibitor. As such, infigratinib is not expected to have a clinically relevant effect on drugs metabolized by CYP3A4. However, due to the weak inhibition, drugs that are CYP3A4 substrates and have a narrow therapeutic index should be co-administered with caution.

Please refer to the current Investigator's Brochure for more details.

2 RATIONALE

2.1 Study rationale and purpose

The growing understanding of the genetic alterations involved in the tumorigenesis of cholangiocarcinoma provides new therapeutic options for molecular targets. Among other genetic alterations, recurrent gene fusions involving the FGFRs are an important class of driver mutations in a number of tumor types, including cholangiocarcinoma.

Recently, Wu (2013) reported 24 primary tumors or cell lines with FGFR1, FGFR2, or FGFR3 fusions among other targetable gene fusions. These FGFR fusions involve numerous protein partners with various functions, which maintain kinase activity after formation. The identified gene fusions expressed an FGFR family member as a 5' or 3' fusion partner with an intact kinase domain, thus suggesting that these may serve as potential actionable therapeutic targets via kinase inhibition. Cancer types harboring FGFR fusions were quite diverse and included cholangiocarcinoma (n=2), breast cancer

(n=4), prostate cancer (n=1), thyroid cancer (n=1), lung squamous cell carcinoma (n=6), bladder cancer (n=5), oral cancer (n=1), head and neck squamous cell carcinoma (n=2), and glioblastoma (n=2). Two cholangiocarcinoma patients were reported to harbor FGFR2-BICC1 fusions. Cells harboring FGFR fusions showed enhanced sensitivity to the FGFR inhibitors PD173074 and pazopanib, suggesting that patients with cancer with FGFR fusions may benefit from targeted FGFR kinase inhibition (Wu 2013).

In a second study (Arai 2013), two fusion kinase genes, FGFR2-AHCYL1 and FGFR2-BICC1 were identified in 2 of 8 cholangiocarcinoma tumor samples by massive-parallel whole transcriptome sequencing. Further, RT-PCR and Sanger sequencing analysis of 102 cholangiocarcinoma specimens (66 intrahepatic cholangiocarcinoma (ICCs) and 36 extrahepatic cholangiocarcinoma (ECCs) identified seven FGFR2-AHCYL1-positive and two FGFR2-BICC1-positive cases, which were identified as oncogenic in an NIH3T3 transformation assay. Treatment with FGFR inhibitors, including BGJ398, reversed the transformed phenotype. In a third study (Jiao 2013), somatic mutations in FGFR2 were identified in 4 of 32 (12.5%) intrahepatic cholangiocarcinomas. Thus, FGFR fusions or activating mutations could potentially identify a subset of cholangiocarcinoma patients who would benefit from targeted FGFR kinase inhibition.

The selective FGFR inhibitor BGJ398 has been shown to specifically inhibit proliferation of cancer cells with FGFR genetic alterations; BGJ398 did not alter cell growth in cells that did not express FGFR or FGFR was not altered. *In vivo*, BGJ398 significantly inhibited growth of tumors in a dose-dependent manner in various mouse and rat xenograft subcutaneous or orthotopic models. These include models of bladder cancer with FGFR3 chromosomal rearrangement or FGFR3 mutation (RT112, MGHU3), endometrial cancer with FGFR2 mutation (AN3CA), lung cancer with FGFR1 amplification (NCI-H1581) and gastric cancer with FGFR2 amplification (SNU16). In addition, a cholangiocarcinoma patient harboring an FGFR2 gene fusion treated with BGJ398 on the BGJ398X2101 study experienced tumor shrinkage.

Thus, on the basis of the activity of BGJ398 in a variety of cancer models harboring FGFR genetic alterations (Guagnano 2012), BGJ398 could be used to treat patients with cholangiocarcinoma whose tumors harbor FGFR genetic alterations, including the recently recognized oncogenic gene fusions.

Based on these data, the current study will treat cholangiocarcinoma patients whose tumor have been found to harbor oncogenic FGFR2 fusions or other FGFR genetic alterations, which are likely to confer sensitivity to BGJ398.

2.2 Rationale for the study design

There is no established second line therapy for cholangiocarcinoma that provides patients with meaningful clinical benefit. Response rates for non-targeted therapy in this patient population have routinely been in the single digits (Valle 2010). On the basis of the activity of BGJ398 in a variety of cancer models harboring FGFR genetic alterations (Guagnano 2012), including translocations, a robust anti-tumor activity of BGJ398 is expected in patients harboring FGFR2 gene fusions or translocations. Thus, a single arm

study evaluating response to BGJ398 and durability of response is an appropriate design in this patient population.

This study is designed to evaluate efficacy of the targeted, selective FGFR 1-3 inhibitor BGJ398 when administered as a single agent to patients with genetically selected advanced or metastatic cholangiocarcinoma through estimation of the overall response rate and to gain further understanding of the role of FGFR genetic alterations including gene fusions in this rare patient population. In addition, molecular characterization of these tumors at baseline and at the time of progression may allow for increased understanding of potential treatment combinations, as well as primary and acquired resistance mechanisms.

Cohort 1 will enroll approximately 120 patients with advanced or metastatic cholangiocarcinoma who have evidence of radiologic progression following a cisplatin- and gemcitabine-containing regimen for advanced disease or a gemcitabine-containing regimen for those who are considered intolerant to cisplatin. This cohort includes approximately 106 patients with FGFR2 gene fusions or translocations and 14 patients with FGFR genetic alterations other than FGFR2 gene fusions or translocations who were enrolled before amendment 2.

Cohort 2 will enroll approximately 20 patients with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations other than FGFR2 gene fusions or translocations (specifically FGFR1, 2, or 3 activating mutation or FGR1 or 3 fusions or translocations) who have evidence of radiologic progression following a cisplatin-and gemcitabine-containing regimen for advanced disease or a gemcitabine-containing regimen for those who are considered intolerant to cisplatin. While FGFR2 fusions are the predominant FGFR genomic alteration seen in cholangiocarcinoma, other FGFR alterations do occur. In Cohort 1, 14 patients were enrolled with non-FGFR2 fusions, including 7 with FGFR1, 2, or 3 amplifications and 7 with FGFR2 mutations. In the 7 patients with FGFR2 mutations and response data, 6 (86%) had stable disease (based on central review). Patients such as these with other FGFR alterations have no targeted treatment options, and these preliminary results compare favorably with outcomes for current standard of care. Therefore, Cohort 2 will enroll patients with known FGFR1, 2, or 3 activating mutation (See Appendix 4 [Section 14.4] for details of allowed mutations) or FGFR1 or 3 fusions or translocations.

Cohort 3 will enroll up to approximately 20 patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations after previous treatment with gemcitabine-containing regimen followed by progression on an FGFR inhibitor (excluding BGJ398). As multiple FGFR inhibitors (both selective and non-selective) have entered into clinical development, it is important to understand the clinical efficacy when compounds are used in sequence. Consideration of the diverse mechanisms of action and binding pocket interactions for FGFR inhibitors suggests that BGJ398 may have activity when used after other FGFR inhibitors (both selective and non-selective). The potential for activity of BGJ398 in this population with limited therapeutic options supports study of BGJ398 in patients after treatment with and progression on other FGFR inhibitors. Approximately 10 patients will initially be enrolled and an additional

10 patients will be added if ≥4 patients of the 10 are assessed to be benefiting from study treatment as defined in Section 10.8.2.

2.3 Rationale for dose and regimen selection

Patients enrolled in all cohorts of this study will receive 125 mg qd of BGJ398 on a 3 week on (21 day) /1 week off (7 day) schedule in 28-day cycles. This dose level and regimen is based on experiences from the CBGJ398X2101 trial.

The MTD/RP2D from the CBGJ398X2101 study was identified as 125 mg administered once daily (qd) in continuous 28-day cycles. While dose levels of 100 mg qd and higher were tolerated by patients, the majority of the patients experienced reversible hyperphosphatemia, which led to study drug interruptions. An evaluation of the drug administration records for patients prior to receiving prophylactic phosphate-lowering therapy, indicated that the median time until first dose interruption was approximately 23 days and the median duration of interruption was 7 days. This observation led to the introduction of an expansion arm in the ongoing CBGJ398X2101 study to evaluate the administration of 125 mg qd on a 3 week on (21 days) / 1 week off (7 days) schedule in 28-day cycles. To date, the majority of patients enrolled in this arm have completed their first cycle of therapy without hyperphosphatemia induced dose interruptions, while maintaining anti-tumor activity.

According to amendment 2, the final market image version 3 (FMI III) formulation of BGJ398 replaced FMI I. These two formulations have been previously compared in two separate studies [CBGJ398X2103 and CBGJ398X2106] to the clinical service form which was used to establish MTD of BGJ398 at 125 mg qd [CBGJ398X2101]. Cross-study comparison of the exposures (AUC and C_{max}) between FMI III and FMI I indicated that exposure of BGJ398 from the FMI III formulation is about 21-35% higher than that of FMI I (21% for AUC_{inf}, 29% for C_{max} and 35% for AUC_{last}). Although BGJ398 has demonstrated high interpatient variability in exposure at the 125 mg dose, on average, steady-state concentrations provide target coverage over the dosing interval at doses associated with efficacy. As observed events with BGJ398 are readily monitorable and considered manageable, patient's doses can be individually titrated to maximize therapeutic potential and minimize toxicity across a wide exposure range. Thus, the dose of FMI III 125 mg qd should pose no additional safety concerns. However, pharmacokinetics, safety and tolerability data from the first 20 patients treated with FMI III up to the end of cycle 1 of treatment will be assessed and compared with the historical data from patients treated with FMI I. Upon review of the data, it may be decided to continue dosing all subsequent patients at 125mg or at a lower dose. All decisions will be made by the QED Therapeutics study team in conjunction with the Investigators. Serial blood samples will also be collected from the remaining patients in this study to further characterize the pharmacokinetic properties of FMI III in this patient population.

According to amendment 4, the final market image version 4 (FMI IV) formulation of BGJ398 will be used for patients in Cohorts 2 and 3. Additionally, patients in Cohort 1 will be transitioned for FMI IV when this formulation is available at the study site. Pharmacokinetics, safety, and tolerability data from all available patients in Cohorts 2

and 3 treated with FMI IV up to the end of cycle 1 of treatment will be assessed and compared with the historical data from patients treated with FMI III.

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described in Table 1 below.

Table 1: Objectives and related endpoints for Cohort 1 and overall study

Objective	Endpoint	Analysis
Primary (Cohort 1)		
To evaluate the efficacy of single agent BGJ398 in patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations or other FGFR genetic alterations	Overall response assessed by central imaging review as per RECIST v1.1	Refer to Section 10.4
Secondary		
Cohort 1: To further evaluate the efficacy of single agent BGJ398	Overall response assessed by investigator; progression free survival, best overall response, disease control assessed by investigator and by central imaging review as per RECIST 1.1; and overall survival	Refer to Section 10.5.1
Cohort 1: To characterize the safety and tolerability of single agent BGJ398	Safety: Type, frequency, and severity of AEs and SAEs; Tolerability: dose interruptions, reductions and dose intensity	Refer to Section 10.5.2
Overall study: To determine selected trough and 2-hr or 4-hr plasma concentrations of BGJ398 and its metabolites To characterize the pharmacokinetic profile of BGJ398 FMI III and FMI IV formulations	Selected trough and 2-hr or 4-hr plasma concentration profile and derived PK parameters of BGJ398 and its metabolites For FMI III and FMI IV: Plasma concentration profile and derived PK parameters of FMI III and FMI IV	Refer to Section 10.5.3
Exploratory (Overall Study)		
To assess markers that may correlate with genetic alterations in tumor tissue at baseline, predictions of response and/or resistance (e.g. gene mutations, amplifications, deletion and/or altered protein expression or activation)	DNA sequencing of paired biopsies (tumor tissue) from patients who progressed and analysis of cell free tumor DNA Serial serum CA19-9 levels	Refer to Section 10.6

Table 2: Objectives and related endpoints for Cohorts 2 and 3

Exploratory Objectives	Endpoint
To characterize the safety and tolerability of BGJ398 in patients with advanced or metastatic cholangiocarcinoma with…	Safety: Type, frequency, and severity of AEs and SAEs;
Cohort 2: …FGFR genetic alterations other than FGFR2 gene fusions or translocations	Tolerability: dose interruptions, reductions and dose intensity

Exploratory Objectives	Endpoint
Cohort 3: …FGFR2 gene fusions or translocations who have received prior FGFR inhibitors	
To evaluate the efficacy of single agent BGJ398 in patients with advanced or metastatic cholangiocarcinoma with… Cohort 2: …FGFR genetic alterations other than FGFR2 gene fusions or translocations Cohort 3: …FGFR2 gene fusions or translocations who have received prior FGFR inhibitors	Progression free survival, overall response, best overall response, response onset, and disease control assessed by investigator as per RECIST v1.1, and overall survival

4 STUDY DESIGN

4.1 Description of study design

This is a multi-center, open label, phase II study evaluating BGJ398 anti-tumor activity in advanced or metastatic cholangiocarcinoma patients with FGFR genetic alterations. All patients will receive BGJ398 once daily on a three week on (21 days), one week off (7 days) schedule in 28-day cycles. Up to approximately 160 patients in total will be enrolled on the study.

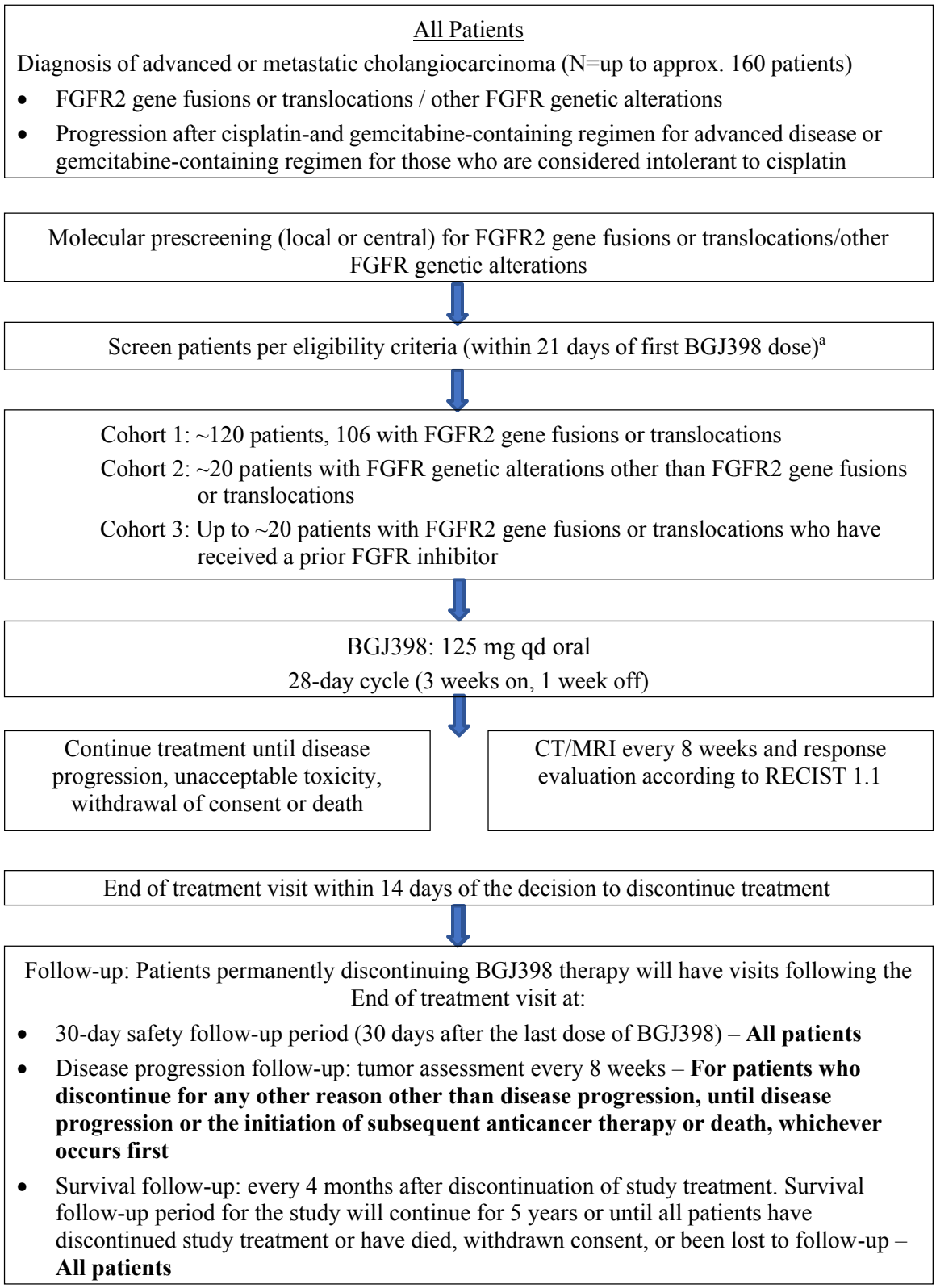
The study has 3 cohorts. Cohort 1 will have approximately 120 patients with advanced or metastatic cholangiocarcinoma: 106 with FGFR2 gene fusions or translocations and 14 with other FGFR genetic alterations enrolled under the original protocol and amendment 1.

Cohort 2 will have approximately 20 patients with advanced or metastatic cholangiocarcinoma with specific FGFR genetic alterations (refer to Section 5.2).

Cohort 3 will have up to approximately 20 patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations who have received a prior FGFR inhibitor excluding BGJ398 (infigratinib). Unlike Cohorts 1 and 2, patients are allowed to have previous treatment with an FGFR inhibitor (either selective [excluding BGJ398] or nonspecific), as long as the required washout of at least 5 half-lives is met.

In order to assess the antitumor activity of BGJ398, patients in all cohorts will be evaluated for tumor response radiographically every 8 weeks until disease progression or discontinuation from study using RECIST 1.1 criteria.

Figure 1: Study Design



[a] Screening assessments are to be completed within 21 days prior to the first dose of treatment, except for the radiological tumor assessment, which can be performed within 28 days prior to the first dose.

Molecular pre-screening

Documented evidence of FGFR2 gene fusions or translocations or other FGFR genetic alterations is required in order to begin study related screening procedures. In addition, the patient may have additional molecular testing performed on the provided tissue sample.

- Evidence can be demonstrated by either locally available data (local laboratory or institution-designated sequencing facility) or through the submission of an archival or newly obtained tumor sample to a QED Therapeutics designated central laboratory for analysis. Tissue requirements are described in Section 7.1.1.

- If local data is not available, the patient must sign the molecular prescreening consent to allow for the collection and/or submission of samples for local testing at an institution designated laboratory or sequencing facility or to the QED Therapeutics designated central laboratory for analysis.

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

Screening

Screening assessments must be completed within 21 days prior to the first dose of study treatment except for the radiological tumor assessment which should be performed within 28 days prior to the first dose (Section 7.1.2).

Treatment period

Treatment period will begin on Cycle 1 Day 1 and will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, or death (Section 7.1.3).

End of treatment (EOT)

The EOT visit occurs within 14 days after of the decision to discontinue study treatment (Section 7.1.4). All participating patients must complete this visit even if they had to discontinue prematurely.

Follow-up

All patients will be followed up as described in Section 7.1.6.

30-day safety follow-up period

At a minimum, all patients must complete the safety follow-up assessments 30 days after their last dose of BGJ398 (Section 7.1.6).

Disease progression follow-up period

All patients enrolled in the study who discontinue study treatment for any reason other than disease progression will have a tumor assessment 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 for survival at least every 4 months for up to 5 years after discontinuation of treatment (Section 7.1.6).

4.2 Timing of interim analyses and design adaptations

Safety and efficacy data will be continuously monitored by QED Therapeutics in conjunction with the investigators for decision-making purposes.

For Cohort 1, one analysis was performed before amendment 2 based on the 61 patients enrolled in the study (30 Jun 2016). Protocol amendment 2 restricted enrollment to patients with FGFR2 fusions or translocations, and the formulation was changed from FMI I to FMI III.

After 20 patients had been treated with FMI III (for at least one cycle) based on amendment 2, a comprehensive review of all relevant data such as PK, safety, dose interruptions/reductions, and available efficacy was performed. Upon review of the data, it was decided to continue dosing all subsequent patients treated with FMI III at 125mg on a 3 weeks on, 1 week off schedule.

In addition, two formal interim analyses for Cohort 1 are planned after amendment 3:

- The first was conducted when the patients enrolled prior to amendment 2 and the patients in Cohort 1 with planned extensive PK sample collection (regardless of whether extensive PK samples were actually collected) had been followed up for at least 10 months after their initial exposure to BGJ398.

- The second will be conducted when all the patients who received BGJ398 at the time of the first formal interim analysis have at least 10 months follow-up after their initial exposure to BGJ398.

Additionally, for Cohorts 2 and 3, review of data will be performed after a total of 15 patients in either Cohort 2 or 3 have been treated with FMI IV for at least one cycle. A formal interim analysis will be conducted for Cohort 3 when the first 10 patients who receive study treatment have the potential to complete their second scheduled scan; this analysis is to determine if an additional 10 patients will be added to the cohort (see Section 10.8.2).

4.3 Assessment of potential mechanisms of resistance

Patients may have tumor tissue and blood samples collected at baseline and at disease progression to study the mechanisms of drug treatment resistance.

4.4 Definition of end of the study

End of study is defined as the time when the last patient completes the survival follow-up as described in Section 7.1.6 and/or when the study is terminated early.

4.5 Early study termination

The study can be terminated at any time for any reason by QED Therapeutics. Should this be necessary, the patient should make every effort to complete their final visit. The same assessments should be performed as described in Section 7.1.4 and Section 7.1.5 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.

5 POPULATION

5.1 Patient population

Adult patients with histologically or cytologically confirmed advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations or other FGFR genetic alterations will be enrolled. Patients must have received at least one prior regimen containing gemcitabine with or without cisplatin for advanced/metastatic disease. Patients should have had evidence of progressive disease following their prior regimen or if prior treatment was discontinued due to toxicity must have continued evidence of measurable disease.

Evidence of FGFR2 gene fusion or other FGFR genetic alterations must be documented through either institutional data or central laboratory testing (please refer to Section 7.1.1 for further details).

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. Patients who do not initially meet all of the inclusion or exclusion criteria may be re-screened for consideration in the trial. If a patient is rescreened, the same patient ID number should be used (see Section 7.1.2.2).

Only patients who have documented evidence of FGFR2 gene fusion or other FGFR genetic alterations will be allowed to enter screening. 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 into all cohorts of this study have to meet **all** of the following criteria, unless otherwise noted:

1. Patients with histologically or cytologically confirmed cholangiocarcinoma at the time of diagnosis. Patients with cancers of the gallbladder or ampulla of Vater are not eligible.

2. Written documentation of local laboratory or central laboratory determination of the following FGFR gene alterations from a sample collected before BGJ398 treatment:

    - Cohort 1: FGFR2 gene fusions or translocations.

    - Cohort 2: one of the following:

        a. FGFR1 fusions or translocations.

        b. FGFR3 fusions or translocations.

        c. FGFR1/2/3 mutation known to be an activating mutation and noted in Appendix 4 (Section 14.4; for mutations not listed in Appendix 4, enrollment may be allowed with written pre-approval of the QED Medical Monitor).

    - Cohort 3: FGFR2 gene fusions or translocations.

3. An archival tissue sample must be available with sufficient tumor for central FGFR gene alteration molecular testing if written documentation is provided from a local laboratory, unless agreed upon between QED Therapeutics and the Investigator. However, if an archival tissue sample is not available, a newly obtained (before start of treatment) tumor biopsy may be submitted instead. If written documentation of FGFR gene alteration in tumor tissue is available from the central laboratory, an additional tumor sample does not need to be submitted for central FGFR gene alteration molecular testing. Note: All enrolled patients should have determination of FGFR gene alteration by the central laboratory as confirmation of local laboratory testing, but this central confirmation is not required prior to enrollment in the study.

4. Evidence of measurable disease according to RECIST Version 1.1.

5. Patients must have received at least one prior regimen containing gemcitabine with or without cisplatin for advanced/metastatic disease. Patient should have had evidence of progressive disease following their prior regimen, or if prior treatment was discontinued due to toxicity must have continued evidence of measurable disease.

6. Patients ≥ 18 years of age of either gender.

7. ECOG performance status ≤ 1 (Patients with ECOG performance status of 2 may be considered on a case-by-case basis after discussion with QED Therapeutics).

8. Able to read and/or understand the details of the study and provide written evidence of informed consent as approved by IRB/EC.

9. Recovery from adverse events of previous systemic anti-cancer therapies to baseline or Grade 1, except for:

   a. Alopecia

   b. Stable neuropathy of ≤ Grade 2 due to prior cancer therapy

10. Able to swallow and retain oral medication.

11. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.2.1 Additional inclusion criteria for Cohort 3

12. Documented prior treatment with FGFR inhibitor other than BGJ398/infigratinib.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Prior or current treatment with a mitogen-activated protein kinase (MEK) inhibitor (all cohorts), BGJ398/infigratinib (all cohorts), or selective FGFR inhibitor (Cohorts 1 and 2 only).

2. 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 2 weeks preceding study entry.

3. History of another primary malignancy except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin or any other curatively treated malignancy that is not expected to require treatment for recurrence during the course of the study.

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. Current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, inflammation or ulceration, keratoconjunctivitis, confirmed by ophthalmic examination.

6. History and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium, vascular system, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification.

7. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BGJ398 (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).

8. Current evidence of endocrine alterations of calcium/phosphate homeostasis, eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis etc.

9. Treatment with any of the following anti-cancer therapies prior to the first dose of BGJ398 within the stated timeframes.

    - Cyclical chemotherapy (intravenous) within a period of time that is shorter than the cycle length used for that treatment (eg, 6 weeks for nitrosourea, mitomycin-C)

    - Biological therapy (eg, 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 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

10. Patients who are currently receiving, or are planning to receive during participation in this study, treatment with agents that are known strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration are excluded. (Refer to Appendix 2 for list of prohibited medications). Patients are not permitted to receive enzyme-inducing anti-epileptic drugs

11. Consumption of grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges, or products containing juice of these fruits, within 7 days prior to first dose

12. Insufficient bone marrow function

    - ANC $< 1{,}000/mm^3$ [$1.0 \times 10^9/L$]

    - Platelets $< 75{,}000/mm^3$ [$75 \times 10^9/L$]

    - Hemoglobin < 9.0 g/dL

13. Insufficient hepatic and renal function

- Total bilirubin > 1.5x ULN (for patients with documented Gilbert syndrome, direct bilirubin ≤1.5x ULN and enrollment requires approval by the medical monitor)

- AST/SGOT and ALT/SGPT > 2.5x ULN (AST and ALT > 5x ULN in the presence of liver metastases)

- Serum creatinine > 1.5x ULN and a calculated (using the Cockcroft-Gault formula [Cockcroft 1976]) or measured creatinine clearance of < 45 mL/min

14. Abnormal calcium or phosphorus:

    - Inorganic phosphorus outside of normal limits

    - Total serum calcium (can be corrected) outside of normal limits

    - Calcium-phosphorus product ≥55 mg^2/dL^2

15. Clinically significant cardiac disease including any of the following:

    - Congestive heart failure requiring treatment (NYHA Grade ≥ 2), LVEF < 50% as determined by MUGA scan or ECHO, or uncontrolled hypertension (refer to WHOISH 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 (males and females)

    - History of congenital long QT syndrome

16. 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

17. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using barrier contraception and a second form of highly effective contraception during dosing and for 3 months following the discontinuation of study treatment.

    WOCBP and males whose sexual partners are WOCBP must agree to use barrier contraception and a second form of highly effective contraception (Clinical Trials Facilitation Group 2014; see Appendix 5 [Section 14.5]) while receiving study drug and for 3 months following their last dose of study drug. Alternatively, total abstinence is also considered a highly effective contraception method when this is in

line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

A woman is not of child-bearing potential if she has undergone surgical sterilization (total hysterectomy, or bilateral tubal ligation or bilateral oophorectomy at least 6 weeks before taking study drug) or if she is postmenopausal and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for at least 12 months, with an appropriate clinical profile, and there is no other cause of amenorrhea (eg, hormonal therapy, prior chemotherapy).

18. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months after the last dose of the study drug and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via seminal fluid.

19. Have amylase or lipase >2.0 × ULN.

20. Have any known hypersensitivity to calcium-lowering agents, infigratinib, or their excipients.

6.1.1 Additional exclusion criteria for Cohort 3

21. Known existence of a V564F mutation in the FGFR2 gene.

6 TREATMENT

The investigational drug will be BGJ398 as an oral formulation (hard gelatin capsules).

6.1 Study treatment

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

6.1.1 Dosing regimen

Table 3: Dose and treatment schedule

Study treatment	Formulation	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
BGJ398	FMI I FMI III FMI IV	Hard gelatin capsule(s) for oral use	125 mg (administered as one 100 mg capsule and one 25 mg capsule)	Daily (3 weeks on, 1 week off schedule in 28-day cycles)

6.1.1.1 Instructions for administration of BGJ398

- Patients should be instructed to take the daily dose of BGJ398 in the morning, at approximately the same time each day (24 ± 4 hour interval). Patients will take their first dose of infigratinib at the study center on Cycle 1 Day 1. On the days of PK sampling, patients should not take their study drug dose at home; patients should take their study drug with them to the investigative site where administration of BGJ398 will be supervised and administration time recorded. On PK sampling days after Cycle 1 Day 1, the time of the previous infigratinib administration (ie, the prior day) before the pre-dose PK sample will be recorded in the eCRF. Administration may fall outside of the ±4 hour interval on the days of PK sampling.

- Patients who initiate treatment as of the implementation of amendment 2 will begin treatment using the FMI III form of BGJ398; patients enrolled into Cohorts 2 and 3 under amendment 4 will receive the FMI IV form of BGJ398. Patients who started treatment prior to the implementation of amendment 2 should continue to receive the formulation of BGJ398 that they received at the initiation of treatment until FMI IV is available at the study site. At that time all patients on study will receive FMI IV.

- BGJ398 should be administered in the fasted state at least 1 hour before or 2 hours after a meal.

- 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 the patient forgets to take the scheduled dose in the morning (other than on a day of PK sampling), he/she should not take the dose more than 4 hours after the usual time and should continue treatment the next day. Any such 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. If the vomiting occurs on full PK sampling days within the first 4 hours post-dosing, this event needs to be noted on the dose administration PK eCRF page, as well as on the adverse event page, as appropriate.

- 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 BGJ398, and limit bioavailability. These agents include, but are not limited to, proton pump inhibitors (eg, omeprazole), H2-antagonists (eg, ranitidine) and antacids. If possible, proton pump inhibitors should be avoided due to their long pharmacodynamic effect and replaced with H2-antagonists or antacids. BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.

- Patients must avoid consuming grapefruits, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges, or products containing juice of these fruits, within 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. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drug for subsequent dosing.

6.1.2 Ancillary treatments

Phosphate-lowering treatment, including low phosphate diet and phosphate binding therapy such as sevelamer hydrochloride, should be implemented prophylactically with meals on the first day of study drug initiation and modified as clinically indicated throughout BGJ398 administration. Recommendations for treatment are provided in Table 5, but should be modified as per country or institutional guidelines.

6.1.3 Treatment duration

All patients will receive BGJ398 daily on a three week on (21 days), one week off (7 days) schedule in 28-day cycles. Patients may continue treatment with BGJ398 until the patient experiences unacceptable toxicity, disease progression, treatment is discontinued at the discretion of investigator or withdrawal of consent, or death.

6.2 Dose modifications

6.2.1 Dose modifications 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. All dose modifications should be based on the worst preceding toxicity (Table 5, Table 6). Dosage changes must be recorded on the Dosage Administration Record CRF.

The following guidelines should be applied.

Each patient will be allowed 3 dose reductions according protocol-specified dose modifications for AEs. A QED medical monitor or designee approval is required for the third dose reduction (Table 4).

Following resolution of toxicity to baseline or ≤ Grade 1, treatment is resumed at either the same or lower dose of study drug as per the criteria in Table 5. If treatment is

resumed at the same dose of study drug, and the same toxicity recurs with the same or worse severity regardless of duration, dose must be reduced to the next lower dose level. If treatment is resumed at the lower dose of study drug, and the same toxicity recurs with the same or worse severity, the patient should have a second dose reduction.

Patients who discontinue study treatment for a study related adverse event or an abnormal laboratory value must be followed as described in Section 6.2.2.

Study drug must be permanently discontinued for a delay of >14 days and may only be restarted with written permission of a QED Therapeutics' medical monitor if (1) the delay was not due to an AE that requires permanent study drug discontinuation as provided in Table 5, and (2) the patient has not met other criteria requiring study drug discontinuation in Section 7.1.4, and it is the Investigator's opinion that no safety concerns are present.

Table 4: Dose reduction table

Dose reduction				
	Starting dose level 0	Dose level -1	Dose level -2	Dose level -3
BGJ398	125 mg	100 mg	75 mg	50 mg [a]

[a] Dose reduction to 50 mg requires QED Therapeutics medical monitor approval. Details are provided in the text above.

Table 5: Criteria for interruption and re-initiation of BGJ398 treatment

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Dose Modifications any time during a cycle of therapy
Cardiac disorders	
Cardiac - Prolonged QTcF interval	
Grade 1 and 2: QTcF ≥ 481 msec and ≤ 500 msec (asymptomatic)	Maintain dose level of BGJ398 Two additional electrocardiograms (ECGs) separated by at least 5 minutes should be performed to confirm the finding. If the finding is confirmed, single ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1, or as clinically indicated. If abnormality is detected, 2 additional ECGs separated by at least 5 minutes should be performed to confirm the finding. • If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per the 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 > 500 msec as identified on the ECG by the investigator	Hold BGJ398. Two additional ECGs separated by at least 5 minutes should be performed to confirm the finding. If the finding is confirmed, monitor patient with hourly ECGs until the QTcF has returned to baseline and 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 Single ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1 or as clinically indicated. If abnormality is detected, 2 additional ECGs separated by at least 5 minutes should be performed to confirm the finding. • If ECG assessments show no QTcF ≥ 481 msec, ECG monitoring will be performed as per the visit schedule for subsequent cycles.

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Dose Modifications any time during a cycle of therapy
	• 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 treatment.
Grade 4: QTcF >500 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Discontinue BGJ398. If QTcF >500 msec or >60 msec change from the baseline is observed, a plasma sample for determination of BGJ398 concentration should be obtained with the time of sample collection noted.
Cardiac disorders - others	
Grade ≥ 3, or congestive heart failure ≥ 2	Discontinue patient from study treatment.
Investigations-Hematology	
Neutrophil count decreased (Neutropenia)	
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1or baseline, then • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If resolved between > 7 days and 14 days, ↓ 1 dose level of BGJ398. • If not resolved within ≤14 days, discontinue patient from study treatment.
Grade 4 (ANC < 0.5 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE ≤ Grade 1, ↓ 1 dose level of BGJ398. If not resolved within ≤14 days, discontinue patient from study treatment.
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)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then • If resolved within ≤ 7 days, ↓ 1 dose level of BGJ398. • If not resolved within 7 days discontinue patient from study drug treatment.
Grade 4	Discontinue patient from study treatment.
Anemia	
Grade 3 (hemoglobin <8.0 mg/dL)	Hold dose of BGJ398 until resolved or corrected to CTCAE Grade ≤ 1 or baseline, then maintain dose level
Grade 4	Hold dose of BGJ398 until resolved or corrected to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Dose Modifications any time during a cycle of therapy**
Platelet count decreased (Thrombocytopenia)	
Grade 3 (platelet < 50 - 25 x 10^9/L) without Grade ≥2 bleeding	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If resolved between > 7 days and 14 days, ↓ 1 dose level of BGJ398 • If not resolved within ≤14 days, discontinue patient from study treatment.
Grade 3 (platelet < 50 - 25 x 10^9/L) with Grade ≥2 bleeding or Grade 4 (platelet < 25 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level. If not resolved within ≤14 days, discontinue patient from study treatment.
Investigations – Renal	
Serum creatinine	
Creatinine clearance <45 mL/min (calculated or measured)	Hold BGJ398 until creatinine clearance is ≥45 mL/min regardless of grade.
Serum creatinine Grade 2 (≥1.5 - 3.0 x ULN or 1.5-3.0 × baseline)	Hold dose of BGJ398 until resolved to Grade ≤1 or baseline: • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If resolved between > 7 days and 14 days, ↓ 1 dose level of BGJ398. • If not resolved within ≤14 days, discontinue patient from study treatment.
Serum creatinine Grade ≥2	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.
Serum creatinine Grade ≥ 3 (> 3.0 x ULN or >3 × baseline)	Discontinue patient from study treatment.
Investigations – Hepatic	
Blood bilirubin (for patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only)	
Grade 2 (> 1.5 - 3.0 x ULN)	Hold dose of study drug until resolved to CTCAE Grade ≤ 1 • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If not resolved within ≤ 7 days, ↓ 1 dose level of BGJ398
Grade ≥3 (> 3.0 x ULN)	Discontinue patient from study treatment.

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Dose Modifications any time during a cycle of therapy**
	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 within ≤ 7 days, ↓ 1 dose level of BGJ398. • If not resolved within ≤ 7 days, discontinue patient from study treatment.
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 both transaminases and bilirubin resolved to CTCAE Grade ≤ 1 or baseline • If resolved within ≤ 7 days, ↓ 1 dose level of BGJ398. • If not resolved within ≤ 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	
General Comment	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 3 (> 2.0 - 5.0 x ULN)	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 2. • ↓ 1 dose level of BGJ398. • If not resolved within ≤14 days, discontinue patient from study treatment. For recurrent Grade 3 asymptomatic lipase or amylase elevation despite dose reduction, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ Grade 2.
Grade 4 (>5.0 x ULN)	For any Grade 4 asymptomatic lipase or amylase elevation, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ Grade 2.

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Dose Modifications any time during a cycle of therapy
Hypophosphatemia	
Serum phosphorus <LLN-2.0 mg/dL (0.6 mmol/L)	Maintain dose level of BGJ398; decrease or hold dose of phosphate binder and optimize standard diet or medical therapy as clinically indicated to increase phosphate level.
Serum phosphorus <2.0-1.0 mg/dL (<0.6-0.3 mmol/L)	• Hold dose of BGJ398 until resolved to >2.0 mg/dL (>0.6 mmol/L). • ↓ 1 dose level of BGJ398. If not resolved within ≤14 days, discontinue patient from study drug.
Serum phosphorus <1.0 mg/dL (<0.3 mmol/L) (life threatening consequences)	Discontinue patient from study drug.
Hyperphosphatemia	
Serum phosphorus > 5.5 – 7.5 mg/dL	Maintain dose level of BGJ398 and optimize phosphate lowering therapy as clinically indicated
Serum phosphorus > 7.5 mg/dL for more than 7 days despite maximal phosphate-lowering therapy **Or**, Single serum phosphorus > 9.0 mg/dL regardless of duration or dose of phosphate lowering therapy. (Optimize/maximize dose and schedule of phosphate lowering therapy in accordance with package insert, country or institutional guidelines.)	Hold BGJ398 dose until resolved to serum phosphorus ≤ 5.5 mg/dL: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 > 7.5 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 nonhyperphosphatemia adverse events.
Serum phosphorus with life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Discontinue patient from study drug
Hypercalcemia	
Serum calcium Grade 2	Hold BGJ398 dose until resolved to Grade 1 or baseline: • if resolved within ≤ 7 days after suspending BGJ398, maintain dose level.

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Dose Modifications any time during a cycle of therapy**
	• if resolved between > 7 days and 14 days after suspending BGJ398, ↓ 1 dose level. • if not resolved within ≤14 days, discontinue patient from study treatment.
Serum calcium Grade ≥3	Discontinue patient from the study treatment
Nervous system disorders	
Neurotoxicity	
Grade 2	Omit dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398. If not resolved within ≤14 days, discontinue patient from study drug.
Grade ≥ 3	Discontinue patient from study drug treatment
GI disorders	
Pancreatitis	
Grade ≥ 2	Discontinue patient from study drug treatment
Diarrhea	
General Comment	Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea
Grade 1	Maintain dose level of BGJ398, initiate anti-diarrheal treatment
Grade 2	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment. • 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 antidiarrheal treatment, discontinue patient from study treatment.
Grade 4	Discontinue patient from study treatment.
Vomiting	
Grade 2 not controlled by optimal anti-emetic therapy	Hold BGJ398 doses until ≤ Grade 1, ↓ 1 dose level.

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Dose Modifications any time during a cycle of therapy**
	If not resolved within ≤14 days, discontinue patient from study treatment.
Grade 3 not controlled by optimal anti-emetic therapy or Grade 4	Discontinue patient from study treatment.
Eye Disorders (confirmed by ophthalmic examination)	
Retinal disorders	
Grade 2 central serous retinopathy and central serous retinopathy - like events	Hold BGJ398 until resolved to ≤ Grade 1 and continue ophthalmic evaluation • If resolved within ≤ 14 days, ↓ BGJ398 by 1 dose level • If resolved after > 14 days, discontinue BGJ398
Grade 3 central serous retinopathy and central serous retinopathy-like events and any other Grade 3 eye disorders	Hold BGJ398 until resolved to Grade ≤ 1. • If resolved within ≤ 14 days, ↓ BGJ398 by 1 dose level • If resolved after > 14 days, discontinue BGJ398
≥ Grade 1 retinal vein occlusion, Grade 4 central serous retinopathy and central serous retinopathy-like events, and Grade 4 other eye disorders	Discontinue patient from study treatment.
Other ocular/visual toxicity	
≥ Grade 3	Hold BGJ398 until resolution to ≤ Grade 1 • If resolution within ≤14 days, ↓ 1 dose level • If resolved after >14 days, discontinue BGJ398
General disorders	
Fatigue	
Grade ≥3	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If resolved after > 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. If not resolved within ≤14 days, discontinue patient from study treatment.
Grade 4	Discontinue patient from study treatment.
All dose modifications should be based on the worst preceding toxicity. Patients may have a third dose reduction only with approval of a QED Therapeutics' medical monitor or designee.	

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. Further guidelines and dose modifications for the management of specific study drug induced toxicities (hyperphosphatemia, diarrhea) are provided in Table 5. All patients must be followed up for adverse events and serious adverse events for 30 days following the last doses of BGJ398.

6.2.3 Anticipated risks and safety concerns for 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, renal toxicities are provided in Table 5. Refer to nonclinical toxicity and or clinical data found in the BGJ398 Investigator's Brochure.

Treatment of adverse events or laboratory abnormalities should follow the protocol where specified. If not specified in the protocol, treatment of AEs or laboratory abnormalities should be according to local institutional guidelines.

6.3 Concomitant medications

The patient must notify the investigational sites 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 eCRF page. All cancer medications/therapies given to the patient after the last dose of study drug must be recorded in the eCRF Cancer Medications/Therapies page until patient is off study. A concomitant medication is considered prohibited if it appears on any of the prohibited medication lists for any clinical pharmacology property of the drug (e.g. CYP, BCRP).

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.

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 as per the label 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.

Management of Hyperphosphatemia

Hyperphosphatemia is a recognized on-target effect of potent and selective inhibitors of the FGFR pathway. While on BGJ398, patients should avoid foods that are especially high in phosphate and, if possible, should restrict dietary phosphate to 600 – 800 mg/day. High-phosphate foods include dairy products; meats, nuts, and other high-protein foods; processed foods; and dark colas.

Patients who have experienced hyperphosphatemia should take a phosphate binder such as sevelamer, sucroferric oxyhydroxide, lanthanum carbonate, ferric citrate, etc. within 30 minutes of a meal on the day while taking BGJ398. Once the patient has had hyperphosphatemia, the patient should remain on a low phosphate diet, if possible, and take phosphate binder on the days BGJ398 is taken, even if the serum phosphorus is normalized. Unless otherwise specified by the local package insert or institutional practice, the following regimen should be used to manage hyperphosphatemia:

- For serum phosphorus >5.5 – 7.5 mg/dL
    - Start sevelamer 800 mg three times a day with meals
    - Increase the dose of sevelamer up to 1200 mg every 8 hours
- For serum phosphorus ≥7.5 mg/dL
    - Increase the dose of sevelamer up to 1600 mg (2 tablets per meal) every 8 hours
    - Consider adding acetazolamide two to three 250 mg tablets per day.

During the BGJ398 cycle, patients do not need to be on a low phosphate diet or take a phosphate binder during their 1-week off period unless serum phosphorus is not normalized. Other dose modifications are provided in Table 5, but should be modified as per country or institutional practice.

Management of Diarrhea

Patients should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/anti-motility agents is recommended at the first sign of diarrhea as initial management. Some patients may require concomitant treatment with

more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study drug should be temporarily interrupted or dose reduced according to Table 5.

Management of Bone Metastatic Disease

Treatment of bone metastatic disease with symptomatic standard of care therapy according to institutional guidelines, including prophylactic treatment with bisphosphonates, palliative localized radiation therapy, and symptomatic treatment with steroids and pain medications is allowed. Initiation of other systemic anticancer therapy as described in Section 6.3.3 is not allowed and requires permanent discontinuation of study treatment.

Management of Alopecia, Palmar-Plantar Erythrodysesthesia, Paronychia, and Stomatitis

Recommendations for management (not required per protocol) of alopecia, palmar-plantar erythrodysesthesia syndrome, paronychia (adapted from Segaert 2005), and stomatitis (adapted from Rugo 2017) are provided in Table 6. These are guidelines only and institutional guidelines should be followed where applicable.

Table 6: Recommended Management of Alopecia, Palmar-Plantar Erythrodysesthesia Syndrome, Paronychia, and Stomatitis

Alopecia	
Grade 1	Continue study drug • Minoxidil 5% (OTC) solution or foam once daily to scalp
Grade 2	Continue study drug • Minoxidil 5% (OTC) solution or foam twice daily to scalp • Fluocinonide 0.05% solution daily to scalp
Palmar-plantar erythrodysesthesia syndrome	
Grade 0/1	Continue study drug • Urea 20% or ammonium lactate 12% lotions BID to hands and feet
Grade 2	Continue study drug • Urea 20% or ammonium lactate 12% BID to hands and feet • Fluocinonide 0.05% cream BID to hands and feet
Grade 3	Hold study drug until resolved to Grade ≤1 • Urea 20% or ammonium lactate 12% BID to hands and feet • Fluocinonide 0.05% cream BID to hands and feet
Paronychia	
Grade 1	Continue study drug • Clindamycin 1% solution around and under nails TID • Soak for 15 minutes daily in white vinegar in tap water (1:1)
Grade 2	Continue study drug • Obtain bacterial cultures to confirm sensitivity to antimicrobial • Cefadroxil 500 mg BID or TMP/SMX DS BID for 14 days • Soak for 15 minutes daily in white vinegar in tap water (1:1) • Dermatology consultation
Grade 3	Hold study drug until resolved to Grade ≤1 • Obtain bacterial cultures to confirm sensitivity to antimicrobial • Cefadroxil 500 mg BID or TMP/SMX DS BID for 14 days • Dermatology consultation
Stomatitis	
Grade 1	Continue study drug • Dexamethasone elixir 0.5 mg/mL swish and spit 1 teaspoon (5mL) TID.
Grade 2	Continue study drug • Dexamethasone elixir 0.5 mg/mL swish and spit 1 teaspoon (5mL) TID
Grade 3	Hold study drug until resolved to Grade ≤1 • Dexamethasone elixir 0.5 mg/mL swish and spit 1 teaspoon (5 mL) TID. • Clotrimazole 10 mg lozenges QD

BID=2 times daily; OTC=over-the-counter; QD=once daily; TID=3 times daily; TMP/SMX DS=sulfamethoxazole and trimethoprim

6.3.2 Permitted concomitant therapy requiring caution and/or action

Details for specific medications which require action and/or caution while on study are provided in Appendix 1. The rationale for these medications is provided below.

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 BGJ398, and limit bioavailability. These agents include, but are not limited to, proton pump

inhibitors (eg, omeprazole), H2-antagonists (eg, ranitidine) and antacids. If possible, proton pump inhibitors should be avoided due to their long gastric pH-lowering effect and replaced with H_2-antagonists or antacids. Study drug should be taken ≥2 hours before or 10 hours after dosing with an acid-reducing agent.

Substrates and inhibitors

CYP3A inhibitors and inducers

BGJ398 is a substrate of CYP3A4. Therefore moderate inhibitors and inducers should be used with caution if no other alternative is available. If anticoagulation is required, heparin and/or low-molecular-weight heparins or direct thrombin inhibitors and/or Factor Xa inhibitors that are not metabolized by CYP3A4 (eg, dabigatran, edoxaban) are preferred. If unavoidable, anticoagulants that are CYP3A4 substrates and have a narrow therapeutic index (eg, warfarin sodium or any other coumadin-derivative anticoagulants or certain direct thrombin inhibitors [eg, argatroban] or Factor Xa inhibitors [eg, rivaroxaban]) should be used with caution.

Transporter substrates

In vitro data show that BGJ398 is an inhibitor of BCRP (Breast Cancer Resistance Protein). Medications which are BCRP substrates must be monitored for potential toxicity and may require dose titration or reduction of the medication.

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 de 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 should be used with caution if an alternative is not available.

Medications with a possible or conditional risk of QT/QTc interval prolongation or torsade de pointes

Preliminary data have shown that BGJ398 has no effect on cardiac conduction or ECG intervals (see current version of the BGJ398 Investigator's Brochure). However, medications that have the potential to prolong the QT/QTc interval or induce Torsade de Pointes (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

Details for specific medications prohibited while on study are provided in Appendix 2. The rationale for the restricted medications is provided below.

Other investigational and antineoplastic therapies

Other investigational therapies must not be used while the patient is on the study treatment. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatment must not be given to patients while the patient is on the study medication. If such agents are required, then the patient must be discontinued from study treatment. The only exception is palliative localized radiation therapy for bone metastases with approval by QED Therapeutics' medical monitor.

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.

CYP inducers

Strong inducers of CYP3A4 are prohibited because their usage may 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.

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 QED Therapeutics to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

6.4.2 Treatment assignment or randomization

This is an open-label, single arm study. There will be no randomization required for this study.

6.4.3 Treatment blinding

Treatment is not blinded in 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 drugs as per the protocol. Study drug(s) 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 CRF.

BGJ398 will be supplied as hard gelatin capsules for oral use at dose strengths of 25 and 100 mg. Excipients will include microcrystalline cellulose, lactose monohydrate, hypromellose 2910, crospovidone, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule. BGJ398 will be manufactured under Good Manufacturing Practice for investigational use. The color and appearance of the capsules are outlined below.

Final market image version 3 (FMI III) formulation (Cohort 1):

Physical Attribute	Appearance (color)	Size 3 Capsule: Swedish orange opaque cap and body filled with white to greyish powder (25 mg) Size 1 Capsule: Swedish orange opaque cap and body filled with white to greyish powder (100 mg)

Final market image version 4 (FMI IV) formulation (all cohorts):

Physical Attribute	Appearance (color)	Size 3 Capsule: White opaque body with gray opaque cap, imprinted with a green band on the body and a black band on the cap filled with white to greyish powder (25 mg) Size 1 Capsule: White opaque body with light orange opaque cap, imprinted with a green band on the body and a black band on the cap filled with white to greyish powder (100 mg)

The FMI III formulation will be provided in 28-count bottles, and the FMI IV formulation will be provided in 21-count bottles.

Patients who initially received FMI III will be switched over to FMI IV when FMI IV is available at the study site.

The site pharmacist or designee will dispense the correct number and dose strength of capsules to ensure the patient receives sufficient drug for each 28-day treatment cycle. Study drug will be dispensed to the patient by authorized trained site personnel only.

6.5.1 Study drug packaging and labeling

BGJ398 capsules are packaged in HDPE bottles with child resistant closures. 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.

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, the study treatment 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

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.

On the day of a scheduled visit to the clinic, the patient will take the study drugs under the supervision of the Investigator or designee. The time of dose administrations on days when PK blood samples are drawn must be recorded in the Dosage Administration Record eCRF.

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 on a regular basis, 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 provide access to all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the monitor.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The study drug can be destroyed at the site if permitted by local regulations. Alternatively, the study drug can be destroyed at a third-party depot.

7 VISIT SCHEDULE AND ASSESSMENTS

7.1 Study flow and visit schedule

Table 7 lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. 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 done any time prior to the initiation of the screening.

- Baseline imaging assessments can be conducted within 28 days prior to 1st day of study treatment.

- All other baseline/screening assessments must be performed within 21 days prior to 1st treatment, except for the ophthalmic examination, which should be completed within 14 days prior to first treatment.

- Baseline/screening assessments that are conducted within 3 days prior to 1st treatment can be used to satisfy the day 1 requirement. Every effort must be made to follow the schedule outlined in Table 7.

For all visits, there is a ± 3-day window on assessments to take into account scheduling over weekends and holidays, **if not explicitly specified otherwise**. For post baseline imaging and ophthalmic assessments, a ±7 day window is allowed, except for the first post baseline assessment (+7 day window permitted). There are no visit windows for the trough PK sampling days (sparse PK sample group [Table 10]: Cycle 1 Days 2, 8, 15, and 21; and extensive PK sample group [Table 11]: Cycle 1 Days 2 and 16).

PK samples will be collected according to Table 10 or Table 11. Biomarker sampling will be conducted as outlined in Table 12.

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

Table 7: Visit evaluation schedule for all cohorts

	Category	Protocol Section	Molecular Pre-screening	Screening[a]	Cycle 1						Cycle 2		Cycle 3		Subsequent cycles		End of study treatment	30-day follow-up	Disease Progression follow-up every 8 weeks	Survival follow-up (every 4 months after EOT)
Study Period			**Screening**		**Treatment**												**EOT**	**Follow-up**		
Day of Cycle				**-21 to -1**	**1**	**2**	**8**	**15**	**16**	**21**	**1**	**15**	**1**	**15**	**1**	**15**	**≤14 days of the decision to discontinue the treatment**			
Informed consent for molecular pre-screening if local data are not available	D	7.1.1	X																	
Pre-screening testing if local data are not available	D	7.1.1	X																	
Study Informed Consent (ICF)	D	7.1.2		X																
Demography	D	7.1.2.3	X	X																
Inclusion/exclusion criteria	D	5.2, 5.3, 7.1.2	X	X																
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	Continuous												X	X		
Physical examination	S	7.2.2.1		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		X			
Vital signs	D	7.2.2.2		X	X		X	X		X	X	X	X	X	X		X			
Performance status	D	7.2.2.4		X	X						X		X		X		X			
Ophthalmic assessment	D	7.2.2.5		X				X			X		X		X[b]		X			
Hematology	D	7.2.2.6.1		X	X		X	X		X	X	X	X		X		X			
Chemistry (predose)	D	7.2.2.6.2		X	X		X	X		X	X	X	X		X		X			
Coagulation	D	7.2.2.6.3		X	If clinically indicated															
Urinalysis (microscopic or macroscopic)	D	7.2.2.6.4		X	If clinically indicated															
Pregnancy test	D	7.2.2.6.5		X	X						X		X		X		X			

	Category	Protocol Section	Molecular Pre-screening	Screening[a]	Cycle 1						Cycle 2		Cycle 3		Subsequent cycles		End of study treatment	30-day follow-up	Disease Progression follow-up every 8 weeks	Survival follow-up (every 4 months after EOT)
Study Period			**Screening**		**Treatment**												**EOT**	**Follow-up**		
Day of Cycle				**-21 to -1**	**1**	**2**	**8**	**15**	**16**	**21**	**1**	**15**	**1**	**15**	**1**	**15**	**≤14 days of the decision to discontinue the treatment**			
Tumor response per RECIST 1.1	D	7.2.1		X									X		Day 1 of every odd cycle		X (if not done within 28 days prior)		X (only for pts. who discontinue for any reason other than progression of disease	
Study drug administration	D	6.1			Continuous on a 3 weeks on 1 week off schedule[c]															
12-lead ECG	D	7.2.2.7		X	X	X	X	X			X		X		X		X			
Cardiac imaging (ECHO or MUGA)	D	7.2.2.7		X							X						X			
Adverse Events	D	8.1, 8.2	Continuously throughout the study															X		
Collection of archival paraffin blocks/slides or a newly obtained tumor sample AND pathology report	D	7.2.4.1	X (if local data not available)	X[d]																
Newly obtained tumor sample (if medically feasible)	D	7.2.4.2		X[e]	X (upon disease progression)-optional															
Blood sample for assessment of circulating tumor DNA (cell free DNA) (all samples are predose)	D	7.2.4.3		X							X		X		Day 1 of every odd cycle		X (if not done within 28 days prior)			
Blood for PK (sparse PK group)	D	7.2.3.1			X	X	X	X		X	X	X	X	X		Day 15 Cycles 4- 6				
Blood for PK (extensive PK group)[f]	D	7.2.3.1			X	X		X	X		X		X		Day 1 Cycles 4-6					

	Category	Protocol Section	Molecular Pre-screening	Screening[a]	Cycle 1						Cycle 2		Cycle 3		Subsequent cycles		End of study treatment	30-day follow-up	Disease Progression follow-up every 8 weeks	Survival follow-up (every 4 months after EOT)
Study Period			**Screening**		**Treatment**												**EOT**	**Follow-up**		
Day of Cycle				**-21 to -1**	**1**	**2**	**8**	**15**	**16**	**21**	**1**	**15**	**1**	**15**	**1**	**15**	**≤14 days of the decision to discontinue the treatment**			
Survival follow-up	D	7.1.6																		X
Antineoplastic therapies since discontinuation of study treatment	D	7.1.4																X	X	
Disease progression follow-up	D	7.1.6																	X	

[a] Screening assessments are to be completed within 21 days prior to the first dose of treatment, except for the radiological tumor assessment, which can be performed within 28 days prior to the first dose, and the ophthalmic examination, which should be completed within 14 days prior to first treatment.
[b] Ophthalmic assessments for subsequent cycles (ie, after C3D1) are to be completed at C7D1 and every 4 months after that (ie, C11D1, C15D1, C19D1, etc).
[c] Study drug will be administered in the clinic on the following days (PK sampling days):
Sparse PK sample group (Table 10): C1D1,2,8,15,21; and C2-6 D1 and D15.
Extensive PK group (Table 11): C1D1,2,15,16; and C2-6 D1.
[d] If written documentation of FGFR2 gene fusion or translocation is determined by a pre-existing test or local laboratory, archival tumor tissue from the same biopsy sample used to determine eligibility (or a new tumor biopsy collected before BGJ398 treatment) should be submitted to the central laboratory for confirmation testing within 14 days after the first treatment. Refer to the Laboratory Manual for the sample requirements and processing instructions for central laboratory testing.
[e] Sample will not be collected if a fresh tumor sample has already been collected at baseline for the purpose of DNA sequencing.
[f] The first 20 patients enrolled in Cohort 1 and treated with FMI III and all patients enrolled in either Cohort 2 or Cohort 3 and treated with FMI IV (amendment 4) will follow the extensive PK sampling schedule.

7.1.1 Molecular pre-screening

Evidence of genetic alterations, including FGFR2 gene fusion or other FGFR genetic alterations, can be obtained from pre-existing analysis, local testing of samples at an institution-designated laboratory or an institution-designated sequencing facility, or through the submission of samples to a QED Therapeutics designated laboratory central facility for testing. When possible, pre-existing analysis by local testing should be performed using a clinically validated test in a CLIA-certified (or equivalent) laboratory.

If local or central 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 pre-screening consent form is not needed if the molecular status of the tumor was previously determined. Written documentation of the local FGFR2 test result must be present in the source documentation for review by QED Therapeutics.

For central FGFR molecular testing, the archival or newly obtained tumor sample will be sent to a QED Therapeutics designated lab and the results of the analysis will be communicated to the respective center. Upon positive determination that the sample submitted contains the required FGFR2 gene fusions or translocation (Cohorts 1 and 3), or FGFR1, 2, or 3 activating mutation or FGFR1 or 3 fusions or translocations (Cohort 2), the patient may sign the study's main Informed Consent to begin screening procedures.

Additional testing will be performed to evaluate other genetic alterations related to or thought to be related to cholangiocarcinoma.

A copy of the corresponding pathology report for each set of slides/blocks should be sent to QED Therapeutics designated central laboratory.

FGFR translocation/alterations status must be captured on the appropriate eCRF upon enrollment onto the study after the patient has signed the study's main Informed Consent.

The tumor blocks will be returned, if molecular pre-screening inclusion criteria are not met.

7.1.2 Screening

The IRB/IEC study approved informed consent form (ICF) must be signed and dated before any study-specific 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. Screening assessments must be

completed within 21 days prior to the first dose of treatment except for (1) the radiological tumor assessment, which should be performed within 28 days prior to the first dose, and (2) the ophthalmology examination, which should be completed within 14 days prior to first dose. Screening assessments must be repeated if outside of screening windows.

7.1.2.1 Eligibility screening

After a patient signs the study Informed Consent Form, the investigator or clinical site should determine patient eligibility.

7.1.2.2 Information to be collected for screen failures

Patients who signed a molecular pre-screening ICF but are considered as ineligible after molecular screening, as well as patients who are found not eligible after signing the informed consent form to participate in the treatment phase of the study, will be considered as screening failures, and data will be handled in the same manner. The reason for not being started on study treatment will be entered on the screening phase disposition page. For all screening failure patients, demography, inclusion/exclusion and informed consent information along with the reason for screen failure will be collected. 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). For molecular prescreening failures, only SAEs possibly related to a study procedure will be reported.

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 (FGFR gene fusions or translocation or other FGFR genetic alterations) and details on prior antineoplastic treatments.

7.1.3 Treatment period

The treatment period commences on the first day of the first cycle of BGJ398 and ends after the last dose of BGJ398.

During the study treatment period, patients will be regularly monitored to assess the safety and early anti-tumor activity of treatment. For purpose of scheduling and evaluations, a treatment cycle will consist of 28 days.

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 details of assessments during the treatment period, refer to Table 7.

7.1.4 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

Study treatment must be discontinued under the following circumstances:

- Adverse events that lead to substantial changes in individual risk-benefit considerations
- Dose delay of > 14 days from the intended day of the next scheduled dose, unless otherwise specified in Section 6.2.1, and approval by QED Therapeutics' medical monitor
- Pregnancy
- Protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 7 (end of study treatment visit) and then enter the follow-up epoch. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7 (Lost to follow-up).

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every 8 weeks until documented disease progression, death, lost to follow-up, or withdrawal of consent.

For patients who have documented radiographic disease progression and continue study treatment according to Section 6.2.1, no further imaging or transmittal of images for central imaging assessment is required.

7.1.4.1 Replacement policy

No replacements will be needed.

7.1.5 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

QED Therapeutics will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. dates of telephone calls, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up.

7.1.6 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. Information relating to antineoplastic therapies taken since discontinuation of study treatment and AEs (including concomitant medication taken for ongoing AEs) will be collected for 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 have a tumor assessment every 8 weeks (± 7 days) as detailed in Table 7, until disease progression or the initiation of subsequent anticancer therapies, or death, whichever occurs first. Any newly started antineoplastic therapies during the follow-up period must be recorded on the Antineoplastic therapy since discontinuation eCRF.

Survival follow-up period

All patients enrolled in the study will be followed for survival at least every 4 months after discontinuation of treatment. Survival follow-up will continue for up to 5 years or until all patients have discontinued study treatment or have died, withdrawn consent, or been lost to follow-up.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient (e.g. dates of telephone calls, emails, letters, etc.). A patient should not be considered lost to follow-up until due diligence has been completed.

7.2 Assessment types

7.2.1 Efficacy assessment

Tumor response will be evaluated locally by the investigator according to the guideline (see Appendix 3) based on the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer 2009). Each patient will be evaluated for all potential sites of tumor lesions at screening/baseline and every 8 weeks after starting study treatment until disease progression.

CT (Computed Tomography) /MRI (Magnetic Resonance Imaging) scans will be performed at baseline within 28 days before start of treatment and subsequently every 8 weeks from treatment start until progression of disease.

After baseline, the first assessment should be performed at Cycle 3 Day 1 (+7 day window) and all subsequent assessments should be performed within ±7 days of the scheduled day of assessment. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow-up. If a patient discontinues treatment for reasons other than radiological documentation of progression of disease, an efficacy assessment should be performed at the time of End of Treatment unless a CT/MRI for tumor measurement was performed ≤ 4 weeks earlier.

Chest, abdomen, and pelvis CT scans are required for all patients at baseline. If at baseline, a patient is known to have a contraindication to CT i.v. contrast media or develops a contraindication during the trial, a contrast-enhanced MRI (if possible) of chest, abdomen, and pelvis should be performed. CT/MRI of the brain should be performed if clinically indicated.

For the patients with skeletal lesions suspected at baseline, whole-body bone imaging should be obtained either with a TC99 bone scan or alternatively a NaF CT/ MRI PET scan. Of note, the CT or MRI portion of the scan should only be substituted for the required chest, abdomen, and pelvic CT scans if the CT or MRI is of diagnostic quality and meets all requirements as described in the study imaging guide (ie, oral and IV contrast, slice thickness, and anatomic coverage). Post-baseline, if skeletal lesions were identified at baseline, which are not visible on the chest, abdomen or pelvis CT/MRI scan, bone imaging with either a TC99 bone scan or NaF CT/MRI PET is required at all post-baseline imaging timepoints (every 8 weeks). In all cases that post-baseline bone

imaging is required, the same modality that was used at screening should be used for all post-baseline imaging when possible.

Partial Response (PR) and Complete Response (CR) should be confirmed by repeat assessments performed at least 4 weeks and no later than 6 weeks after the criteria for response are first met.

PET/CT may be used only if it is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media. While FDG-PET may complement CT scans in assessing progression per RECIST 1.1 (Appendix 3) FDG-PET assessments should be disregarded for this protocol.

If possible, a single radiologist should perform all tumor response evaluations for an individual patient.

Any lesion that has been previously treated with radiotherapy should be considered as a nontarget lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a target lesion.

All radiological assessments obtained for patients enrolled in Cohort 1 will be sent to a QED Therapeutics designated central imaging CRO. The site manual provided by the designated imaging CRO will provide further details regarding image collection and central imaging assessment.

7.2.2 Safety and tolerability assessment

Safety and tolerability assessments will include adverse event reporting and changes from baseline in laboratory parameters and vital signs. Tolerability will be assessed by the incidence of AEs leading to study drug delay or discontinuation. 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.

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.

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

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 in the same position, either sitting or supine, before dosing and as indicated in Table 7.
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

Weight will be measured as indicated in Table 7. 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 will be assessed as indicated in Table 8. Assessments of performance status will be performed on the scheduled day, even if study treatment is being withheld.

Table 8: 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 (eg, 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

7.2.2.5 Ophthalmic assessments

Ophthalmic examination will be performed by an ophthalmologist as indicated in Table 7 (and with any new onset of visual disturbance). For post-baseline assessments, a ±7 day window is allowed, except for the first post-baseline assessment (+7 day window permitted).

Assessments will include: visual acuity testing (including corrected distance acuity), slit lamp examination of the anterior eye segment, IOP, retinal OCT (required with amendment 5), and dilated fundoscopy (required with amendment 5). Additional examination methods such as specular microscopy and corneal pachymetry will be performed as clinically indicated.

Retinal OCT scan images may be collected centrally.

7.2.2.6 Laboratory evaluations

Clinical laboratory analyses are to be performed by the local laboratory as indicated in Table 7 and Table 9. 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 (eg, 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).

QED Therapeutics 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, QED Therapeutics must be provided with a copy of the certification and normal ranges for that laboratory.

7.2.2.6.1 Hematology

Hematology tests are to be performed by the local laboratory according to the visit schedule outlined in Table 7. For details on the hematology panel refer to Table 9.

7.2.2.6.2 Clinical chemistry

Clinical chemistry tests are to be performed by the local laboratory according to the visit schedule outlined in Table 7. For details on the biochemistry panel refer to Table 9.

7.2.2.6.3 Coagulation

International normalized INR, pro-thrombin time (PT), partial thromboplastin time will be measured according to the visit schedule in Table 7 and Table 9.

7.2.2.6.4 Urinalysis

Urinalysis includes dipstick analysis will be performed according to the visit schedule in Table 7 and Table 9. Microscopic urinalysis will be performed only if macroscopic urinalysis result is abnormal.

7.2.2.6.5 Pregnancy and assessments of fertility

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

Table 9: Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Red blood cell count, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Biochemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Calcium (can be corrected), Chloride, Creatinine, Blood Urea Nitrogen (BUN), Potassium, Sodium, Magnesium, Phosphate. Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Lipid profile (Total Cholesterol, Triglycerides), Total Protein, Urea, 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; day 1 of each cycle, EOT and other times points

7.2.2.7 Electrocardiograms and cardiac imaging

ECG evaluations will be conducted centrally. For all patients prior to the first administration of BGJ398, a minimum of 3 sequential 12-lead ECGs, separated by at least 5-10 minutes, must be performed on Day 1 of Cycle 1. This is necessary to get an accurate baseline QTcF calculation. 12-lead ECGs are to be performed at the following time-points:

- At screening and/or baseline
- Cycle 1 Day 1: pre-dose, 2-hr post-dose, ± 15 min, and 4-hr post-dose ± 30 min (3 sequential)
- Cycle 1 Days 2, 8 and 15: pre-dose and 2-hr post-dose, ± 15 min (3 sequential)
- Cycle 1 Day 15: 4-hr post-dose ± 30 min (3 sequential)
- Cycle 2 onwards, day 1 of every cycle: pre-dose (3 sequential)
- At the end of treatment

MUGA scans or echocardiogram to assess LVEF will be performed as outlined in Table 7, within the windows outlined in Section 7.1. A MUGA scan or echocardiogram will be performed at end of study treatment only if an assessment of LVEF has not been performed ≤14 days prior to study completion.

Clinically significant ECG and cardiac imaging findings must be discussed with the QED Therapeutics Medical Monitor prior to enrolling the patient in the study. Clinically significant ECG and cardiac imaging abnormalities present prior to randomization should be reported on the Medical History eCRF page. Significant new findings post

randomization from initiation of study drug until 30 days after permanent discontinuation of study drug must be recorded as an AE on the AE eCRF.

7.2.3 Pharmacokinetics

Blood samples for PK evaluation will be collected from all enrolled patients participating in the study. Time points of blood sample collection for PK are outlined in Table 10 and Table 11.

On the days of pharmacokinetic sampling, patients should take their medication at the clinic immediately after the pre-dose sample is taken. Patients who forget and take their medication at home will be excluded from pharmacokinetic analysis for that day; they should not have blood samples collected. Complete dosing information, including the date and time of actual blood draw and time of the last study drug dose prior to the sampling, should be obtained on all sampling days and recorded on the appropriate blood collection eCRF. If any of the scheduled sampling times are missed or a sample is not drawn according to this schedule, the actual collection date and time will be recorded and the remaining samples will be collected on schedule whenever possible.

If vomiting occurs within 4 hours following study-drug administration on the day of PK blood sampling, the time (using the 24-h clock) of vomiting should be recorded. No additional trial medication should be taken in an effort to replace the material that has been vomited. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the Adverse Events eCRF. If vomiting occurs after taking the drug no re-dosing of the patient is allowed before the next schedule dose.

If any of the following events occurs, an unscheduled PK samples should be collected:

- If a patient treated with investigational drug experiences an AE that results in an unscheduled visit or fits the criteria of a SAE, as determined by the investigator.

- Whenever an ECG with a QTcF change from baseline > 60 ms or a new absolute QTcF ≥ 501ms result is known, an unscheduled blood samples should be collected to assess concentrations of BGJ398 and its metabolites. The exact time of sample collection should be noted in the eCRF.

7.2.3.1 Pharmacokinetic blood sample collection and handling

At the specified time points detailed in Table 10 or Table 11, as appropriate, 3 mL of blood (per sample) will be collected for the measurement of plasma concentrations of BGJ398 and its metabolites.

The first 20 patients enrolled in Cohort 1 and treated with FMI III, and all patients enrolled in Cohort 2 and Cohort 3 and treated with FMI IV, will follow the PK sampling schedule outlined in Table 11.

All blood samples will be taken by central line, direct venipuncture, or an indwelling cannula inserted in a forearm vein. Complete instructions for sampling processing,

handling and shipment will be provided in the Laboratory Manual. Residual plasma samples from this study may also be used for exploratory analysis to further characterize the PK of BGJ398 and/or its metabolites. This may include using leftover samples for protein binding analysis or metabolite profiling (eg, other metabolites and markers for metabolic enzyme activity such as 4- beta hydroxyl cholesterol levels), if there is sufficient sample remaining.

Table 10: Pharmacokinetic blood collection time points for patients (applicable for patients enrolled under amendment 1 and patients on sparse PK sample group)

Cycle	Day	Scheduled time point relative to dosing	Dose reference identification (DRID) No. (BGJ398)	PK Sample No. (BGJ398)	Sample volume (mL)
1	1	Pre-dose[a]	101	101	3
1	1	2 hrs (±15 min) postdose	101	102	3
1	1	4 hrs (±30 min) postdose	101	301	3
1	2	Pre-dose[a] (24 h post day 1 dose ± 120 min)	102, 12*	103	3
1	2	2 hrs (±15 min) post dose	102	104	3
1	2	4 hrs (±30 min) postdose	102	302	3
1	8	Pre-dose[a] (24 h post day 7 dose ± 120 min)	103, 13*	105	3
1	8	2 hrs (±15 min) postdose	103	106	3
1	8	4 hrs (±30 min) postdose	103	303	3
1	15	Pre-dose[a] (24 h post day 14 dose ± 120 min)	104, 14*	107	3
1	15	2 hrs (±15 min) post dose	104	108	3
1	15	4 hrs (±30 min) post dose	104	304	3
1	21	Pre-dose[a] (24 h post day 20 dose ± 120 min)	105, 15*	109	3
2	1	Pre-dose[a]	106	110	3
2	15	Pre-dose[a]	106	305	3
2	15	4 hrs (±30 min) post dose	106	306	3
3	1	Pre-dose[a]	107	111	3
3	15	Pre-dose[a]	107	307	3
3	15	4 hrs (±30 min) post dose	107	308	3
4	15	Pre-dose[a]	108	309	3
4	15	4 hrs (±30 min) post dose	108	310	3
5	15	Pre-dose[a]	109	311	3
5	15	4 hrs (±30 min) post dose	109	312	3
6	15	Pre-dose[a]	110	313	3
6	15	4 hrs (±30 min) post dose	110	314	3
NA	NA	Unscheduled: PK samples related to a QTcF change from baseline > 60 ms and a new absolute QTcF >= 501 ms	NA	1001+	3
NA	NA	Unscheduled Anytime	NA	1051+	3

Note: Patients enrolled under amendment 1 and patients on the sparse PK sample group enrolled before amendment 4 did not have Cycles 1-3 samples taken 4 hours post dose or Cycles 4-6 samples.
a Take PK sample immediately prior to the next administration of BGJ398
* Dose reference ID (DRID) corresponds to previous days dosing time

Table 11: Pharmacokinetic blood collection time points for patients (for first 20 patients treated with FMI III [Cohort 1] and all patients treated with FMI IV [Cohort 2 and 3]: extensive PK group)

Cycle	Day	Scheduled time point relative to dosing	Dose reference identification (DRID) No. (BGJ398)	PK Sample No. (BGJ398)	Sample volume (mL)
1	1	Pre-dose[a]	201[b]/301[c]/401[d]	201/301/401	3
1	1	0.5 hr post dose ± 10 min	201/301/401	202/302/402	3
1	1	1 hr post dose ± 10 min	201/301/401	203/303/403	3
1	1	2 hr post dose ± 15 min	201/301/401	204/304/404	3
1	1	3 hr post dose ± 30 min	201/301/401	205/305/405	3
1	1	4 hr post dose ± 30 min	201/301/401	206/306/406	3
1	1	6 hr post dose ± 30 min	201/301/401	207/307/407	3
1	1	8 hr post dose ± 60 min	201/301/401	208/308/408	3
1	2	Pre-dose[a] (24 hr post day 1 dose ± 120 min)	202, 201*/302, 301*/402, 401*	[a]209/309/409	3
1	15	Predose[a]	203, 203*/303, 303*/ 403, 403*	[a]210/310/ 410	3
1	15	0.5 hr post dose ± 10 min	203/303/403	211/311/411	3
1	15	1 hr post dose ± 10 min	203/303/403	212/312/412	3
1	15	2 hr post dose ± 15 min	203/303/403	213/313/413	3
1	15	3 hr post dose ± 30 min	203/303/403	214/314/414	3
1	15	4 hr post dose ± 30 min	203/303/403	215/315/415	3
1	15	6 hr post dose ± 30 min	203/303/403	216/316/416	3
1	15	8 hr post dose ± 60 min	203/303/403	217/317/417	3
1	16	Pre-dose[a] (24 hr post dose ± 120 min)	204, 203*/304, 303*/404, 403*	[a]218/318/418	3
2	1	Pre-dose[a]	205, 205*/305, 305*/ 405, 405*	[a]219/319/419	3
3	1	Pre-dose[a]	206, 206*/306, 306*/ 406, 406*	[a]220/320/420	3
4	1	Pre-dose[a]	207, 207*/307, 307*/407, 407*	[a]221/321/421	3
5	1	Pre-dose[a]	208, 208*/308, 308*/ 408, 408*	[a]222/322/422	3
6	1	Pre-dose[a]	209, 209*/309, 309*/ 409, 409*	[a]223/323/423	3
NA	NA	Unscheduled: PK samples related to a QTcF change from baseline > 60 ms and a new absolute QTcF ≥ 501 ms	NA	2001+/3001/4001	3
NA	NA	Unscheduled Anytime	NA	2051+/3051/4051	3

[a] Take PK sample immediately prior to the administration of BGJ398, applicable to Cohorts 1-3
[b] Dose reference ID starting with 2 (e.g 201) refers to patients dosed in Cohort 1.
[c] Dose reference ID starting with 3 (e.g 301) refers to patients dosed in Cohort 2.
[d] Dose reference ID starting with 4 (e.g 401) refers to patients dosed in Cohort 3.
* Dose reference ID (DRID) corresponds to previous days dosing time

7.2.3.2 Analytical method

Plasma concentrations of BGJ398 and its active metabolites (BHS697, BQR917, and CQM157) will be measured using a validated liquid chromatography-tandem mass

spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 1.0 ng/mL. Concentrations below the LLOQ will be reported as 0 ng/mL and missing samples will be labeled accordingly. Study samples may be reanalyzed at other QED Therapeutics approved facilities for the determination of long term stability or cross-check between QED Therapeutics approved laboratories. These additional investigations are not considered part of this study and, as such, the results of any such analysis will not be included in the final report.

7.2.4 Biomarkers

BGJ398 biomarker assessments are required to confirm patient eligibility and potentially aid in understanding the effects of BGJ398 treatment on molecular markers of disease and FGFR pathway regulation as related to clinical outcome.

For all cohorts, written documentation of local laboratory or central laboratory determination of FGFR gene alterations from tissue collected before BGJ398 treatment is required.

For Cohort 1 and Cohort 2:

- If eligibility is determined by pre-existing test results or pre-screening by a local laboratory, then tumor tissue sample must be sent to the central laboratory for confirmation of the FGFR genetic alteration. The tumor tissue sent for confirmatory testing should be from the same biopsy sample that was used to determine eligibility.

- If an archival tissue sample is not available, a new tumor biopsy must be obtained before BGJ398 treatment. Refer to the Laboratory Manual for additional details on the amount of tumor tissue required for testing by the central laboratory.

- If written documentation of FGFR genetic alteration in tumor tissue is available from the central laboratory, an additional tumor sample does not need to be submitted for central molecular testing.

For Cohort 3, written documentation of the FGFR2 gene fusion from a clinically-validated test on a sample (tumor tissue or cell-free DNA from blood) collected after treatment with the prior FGFR inhibitor is highly recommended. If written documentation is not available, a tumor sample collected after treatment with the prior FGFR inhibitor may be submitted to the central laboratory but is not required for enrollment.

QED Therapeutics designated lab(s) will be used for processing of all tumor samples collected. The central laboratory will provide kits to collect and ship these samples to QED Therapeutics designated lab(s) for analysis. Details on the collections, shipment of samples are provided to investigators in the laboratory manual.

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (eg, inadequate sample number, issues related to the quality of the sample or issues related to

the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of QED Therapeutics.

Table 12: Biomarker sample collection plan

Sample Type	Tissue Amount	Visit	Time point
Archival tumor tissue and corresponding pathology report (to determine patient's FGFR status)[a] OR Newly obtained tumor sample	A tumor block is preferred or a minimum of 15-20 slides	Molecular pre-screening for central testing Requires Molecular prescreening ICF	Any time prior to starting study-specific screening procedure (patient must have required genetic alteration in order to start screening)
Archival tumor tissue and a corresponding pathology report[b] OR Newly obtained tumor sample if archival sample is not available (highly recommended for Cohort 3).	A tumor block is preferred or a minimum of 15-20 slides.	Screening	Day -28 up to day -1
Optional-Newly obtained tumor sample (if feasible)	Tumor tissue (formalin fixed paraffin embedded) 11-20 unstained slides	For patients who have had a response upon disease progression	Upon disease progression
Blood (plasma) for circulating tumor DNA (cell free DNA) assessment [b]	~ 10.0mL	Screening/ baseline, C2D1, day 1 of every odd numbered cycle and at progression/ end of treatment (should be taken prior to biopsy procedure)	Circulating tumor DNA assessment

[a] Only needed if pre-screening is done by the QED Therapeutics designated lab
[b] Only if not submitted to the central laboratory for FGFR molecular pre-screening

7.2.4.1 Archived tumor samples

Collection of an archival tumor sample (tissue blocks or 11-20 unstained slides) is mandatory and will be collected from all patients at screening if a sample was not submitted to the central laboratory for FGFR molecular prescreening. A corresponding pathology report should be included along with the archival sample. If an archival tumor sample is not available, a newly obtained tumor sample should be obtained and provided as a formalin-fixed, paraffin-embedded block. Archival or newly obtained tumor samples will be used to explore mechanisms of resistance to cancer treatment through analysis of next generation DNA sequencing data from tumor samples at baseline and after the

development of disease progression (whenever available). Additional archival sample may be requested if the original sample sent is of insufficient quantity or quality to complete the planned analysis.

The sample collection must be captured on the appropriate eCRF and requisition page(s). Detailed instructions for the collection, handling, labeling, and shipment of samples are outlined in the CRO Laboratory Manuals.

7.2.4.2 Newly obtained tumor samples

A newly obtained tumor sample should be collected at progression (end of treatment) for patients if safe and feasible, as it will provide a unique opportunity to investigate the potential mechanisms of resistance to BGJ398. This will be performed using a combination of genomic, transcriptomic and proteomic technology, which may include profiling of mutation, amplification and/or modification in DNA, RNA, or protein levels in tumor tissue.

The sample collection must be captured on the appropriate eCRF and requisition page(s). Detailed instructions for the collection, handling, labeling, and shipment of samples are outlined in the CRO Laboratory Manuals.

7.2.4.3 Exploratory biomarkers- cell free DNA assessment

Blood (approximately 10 ml) will be collected at screening, Cycle 2 Day 1, day 1 of every odd numbered cycle at the time of response assessment scans, and at the time of disease progression (EOT). These samples will be used for analysis of cell-free DNA to explore whether genetic alterations found in tumor samples may also be observed in blood, and if any alterations found are predictive of response and/or associated with development of resistance.

Detailed instructions for the collection, handling and shipment of samples are outlined in the [CBGJ398X2204 Laboratory Manual].

7.2.4.4 Optional additional exploratory biomarker assessments using the remaining biomarker samples

Patients will have the opportunity to consent to use of their remaining samples (tissue, tumor DNA, or blood) for additional research related to BGJ398, cancer or other study treatments. This may also include research to help develop ways to detect, monitor or treat cancer. A decision to perform such exploratory biomarker research studies would be based on outcome data or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

Remaining tissue and cell free DNA samples may be subjected to genetic testing (DNA, RNA, protein) to profile genetic alterations in these samples. The investigators and patients will not receive the results from future research. The biological samples will be coded with a unique number that links the samples to the study patient in the study database as part of de-identification of the samples.

The samples may be stored under QED Therapeutics' control or by its authorized agents. The samples will be stored up to 15 years. The period of time that data derived from future research may be used is not specified and these data may be used indefinitely. The data may be shared with Health Authorities worldwide, at medical meetings, or in medical publications. Participation is optional for patients to have their tissue and blood used in future research. Patients can request that QED Therapeutics not use their stored samples for future research, to the extent that they have not already used the sample, and to the extent that they are able to locate the sample after it has been de-identified. Patients who fail prescreening or fail screening will not have their samples stored for future research.

8 SAFETY MONITORING AND REPORTING

8.1 Adverse events

8.1.1 Definition 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. (Adverse events that occur before a patient signs the informed consent are recorded on the Medical History/Current Medical Conditions eCRF.) Adverse events that occur after informed consent is signed and prior to initiation of study treatment will only be captured if they meet the definition of serious adverse events and are reported to be causally related with study procedures (eg, an invasive procedure such as biopsy). All other adverse events occurring after informed consent is signed prior to initiation of study treatment should be recorded as medical history. Adverse event monitoring and recording should be continued for at least 30 days following the last dose of study treatment.

For patients who sign the molecular pre-screening ICF, 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).

Patients with known FGFR2 gene fusions or other FGFR genetic alteration status will only sign the main study ICF and AE collection for these patients will start from the time of signing the main ICF.

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 (CTCAE) version 4.03. 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,

if the patient dies while on study, the death will be captured on the End of Treatment disposition eCRF. If the patient dies while in follow-up, the death will be captured on the End of Study disposition eCRF and if the patient dies post-follow-up and is being followed for survival, their death will be captured on the Survival Follow-up eCRF.
The occurrence of adverse events should be sought by non-directive questioning of the patient 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 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)

3. Its relationship to study drug (reasonable possibility that AE is related: No, Yes)

4. Action taken with respect to study treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

5. Whether medication or therapy was given (no concomitant medication/non-drug therapy given, concomitant medication/non-drug therapy given)

6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

7. Whether it is serious, where a Serious Adverse Event (SAE) is defined as in Section 8.2.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.2.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. 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.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure or will be communicated between IB updates 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.

8.1.1.1 AE reporting of overdose of BGJ398

Overdose of BGJ398 is to be reported as an AE when drug is administered or taken at a dose ≥200 mg and the overdose is associated with signs or symptoms. Overdose should follow the same reporting requirements as SAEs.

8.1.1.2 Hy's Law

Additionally, potential drug induced liver injury that meets the following criteria (elevation of bilirubin and ALT/AST that meet Hy's Law criteria [FDA Guidance for Industry 2009]):

- Treatment-emergent ALT or AST >3 × baseline value in combination with total bilirubin ≥2 × ULN (of which ≥35% is direct bilirubin)
- Treatment-emergent ALT or AST >3 × baseline value in combination with clinical jaundice.

and is suspected or confirmed drug-induced liver injury, according to Hy's law criteria, requires reporting as an SAE.

8.1.1.3 Progression of underlying malignancy should be reported as AE only in special circumstances

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalization **solely** due to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

8.1.2 Laboratory test abnormality

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 (eg, hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).Laboratory abnormalities that constitute an Adverse event in their own right should be recorded on the Adverse Events eCRF. 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 v4.0 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 and is still, by definition, an adverse event.

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, ie, 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, unless hospitalization is for:

    a. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

    b. 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

    c. Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

    d. Social reasons and respite care in the absence of any deterioration in the patient's general condition

In addition, any suspected transmission of an infectious agent via a medicinal product will be considered an SAE at study centers in the EU.

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.

Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

8.2.2 Reporting

For patients whose FGFR2 gene fusions or other FGFR genetic alteration status is unknown, SAE collection will start upon signing the molecular pre-screening ICF. 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. If the main ICF is signed, SAE collection is as below.

Patients with known FGFR2 gene fusions or translocations/other FGFR genetic alteration status who do not sign the molecular pre-screening ICF, SAE collection starts at the time of signing main study informed consent regardless of whether the patient is found to be a screen failure.

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 Covance Safety (email: SAEintake@covance.com; FAX: 1-888-726-8416) within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 days period should only be reported to Covance Safety if the investigator suspects a causal relationship to the study treatment. Any additional information for the SAE including 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 submit the completed form within 24 hours to Covance Safety (email: SAEintake@covance.com; FAX: 1-888-726-8416). Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each reoccurrence, 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 study treatment, a Covance Safety associate may urgently require further information from the investigator for Health Authority reporting. Covance Safety 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 blinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment (and for 30 days after the last study drug dose) must be reported to Covance Safety (email: SAEintake@covance.com; FAX: 1-888-726-8416) 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 of a patient or partner of a male patient should be entered on the Pregnancy Notification CRF and reported by the investigator to Covance Safety (email: SAEintake@covance.com; FAX: +1-888-726-8416). Pregnancy follow-up should be documented on a paper Pregnancy Follow-up Form and reported to Covance Safety as above. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warning and precautions

No evidence available at the time of this writing indicated that special warnings or precautions were appropriate, other than those noted in the current Investigator's 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: a DMC is considered not feasible due to the short duration of the study. However, measures are put in place for monitoring the safety of the patients participating in this part of the study:

- Prompt review of safety data and constant monitoring for emerging safety signals by participating study sites and QED Therapeutics Personnel. As for any other study conducted by QED Therapeutics, any SUSAR and/or new safety signals will be promptly communicated to all participating investigators and Health Authorities.

In lieu of a DMC, regular teleconferences with investigators will be held for reviewing reported safety data during the trial.

8.7 Steering committee

Not applicable.

9 DATA COLLECTION AND MANAGEMENT

9.1 Data confidentiality

All records identifying the patient will be kept confidential and, in accordance with the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the subject number will be recorded on the eCRF. If the patient name appears on any other document or trial materials, then that information must be redacted before a copy of the document is supplied to the sponsor. Trial data stored on a computer will be stored in accordance with local data protection laws and regulations. Patients will be informed in writing that representatives of the sponsor, Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations.

If the results of the trial are published, the patients' identity will remain confidential.

The investigator will maintain a list to enable patients' records to be identified in accordance with applicable laws and regulations.

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.

Either year of birth or exact date of birth (depending on local privacy regulations) will be recorded to establish that the patient 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, QED Therapeutics 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 and 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. QED Therapeutics 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

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. the investigator and 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 eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

PK and biomarker (blood and tissue) samples obtained during the course of the study will be collected from the Investigator sites and analyzed by a QED Therapeutics designated laboratory, contracted central laboratories, or local laboratories. ECG data collected during the study will be reviewed and processed centrally by a specialist CRO. Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. 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

For studies using eCRFs, QED Therapeutics 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. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

PK, and biomarker samples and ECG data will be processed centrally and the results will be sent electronically to QED Therapeutics (or a designated CRO).

The occurrence of any protocol violations will be determined. Once the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Appropriate QED authorization is required prior to making any database changes to locked data.

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 QED Therapeutics and/or designated CRO. Any data analysis carried out independently by the investigator must be submitted to QED Therapeutics 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 and all relevant PK and PD measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

In general, analyses will be done by cohort with subanalyses by formulation (FMI I, III, or IV) or fusion status as appropriate unless otherwise specified.

Two formal interim analyses for Cohort 1 are described in Section 10.7. The primary analysis for Cohort 1 will be conducted when all patients in Cohort 1 have the potential to be followed for at least 10 months after their initial exposure to study treatment.

For Cohorts 2 and 3, review of data will be performed after a total of 15 patients in either Cohort 2 or 3 have been treated with FMI IV for at least one cycle. Primary analysis will be conducted when all patients in the cohorts have the potential to be followed for at least 10 months after their initial exposure to study treatment.

For Cohort 3, one formal interim analysis will be conducted after the first 10 dosed patients in this cohort have the potential to complete their second scheduled scans (approximately 16 weeks from their first dose) to determine if the cohort will be expanded.

The additional data for patients continuing to receive BGJ398 and for patients who remain in safety or survival follow-up beyond the cut-off point for the primary analyses, as allowed by the protocol, will be summarized in a final CSR that will be prepared at the end of the study. In the final CSR, analyses will be done for each cohort. For exploratory purposes, for patients enrolled in Cohort 1 who do not have FGFR2 fusions or translocations, data may be combined and summarized with Cohort 2.

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. 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 Interim Efficacy Analysis Set 1 for Cohort 1

The Interim Efficacy Analysis Set 1 for Cohort 1 includes all patients with planned extensive PK sample collection (regardless of whether extensive PK samples were actually collected) and all patients enrolled prior to amendment 2. Unless otherwise specified, the Interim Efficacy Analysis Set 1 will be used as the primary efficacy analysis set for the first formal interim analysis for Cohort 1 after amendment 3. Patients

will be classified according to their baseline genetic status (FGFR2 gene fusions or translocations only vs other FGFR genetic alterations).

10.1.3 Interim Analysis Set 2 for Cohort 1

The Interim Analysis Set 2 for Cohort 1 includes patients in Cohort 1 with FGFR2 gene fusions or translocations who have received at least one dose of BGJ398. Interim Analysis Set 2 for Cohort 1 will be used as the primary analysis set for the second formal interim analysis for Cohort 1 after amendment 3.

10.1.4 Sensitivity Analysis Set for Cohort 1

The Sensitivity Analysis Set for Cohort 1 includes patients with FGFR2 gene fusions or translocations who received BGJ398 at the time of the first formal interim analysis and patients who have disease progression according to central imaging review or ended treatment by the cutoff date for the second formal interim analysis for Cohort 1 after amendment 3. The cutoff date for the second formal interim analysis is planned so that all the patients with FGFR2 gene fusions or translocations who received BGJ398 at the time of the first formal interim analysis have 10 months follow-up after their initial exposure to BGJ398. The Sensitivity Analysis Set for Cohort 1 will be used for supportive sensitivity analyses for the second formal interim analysis for Cohort 1.

10.1.5 Interim Analysis Set for Cohort 3

The Interim Analysis Set for Cohort 3 will include the first 10 dosed patients who have the potential to complete second scheduled scan.

10.1.6 Per-Protocol Set

The Per-Protocol Set (PPS) will consist of a subset of patients in the FAS who are compliant with requirements of the Clinical Study Protocol (CSP) in the following ways:

- Patient had an adequate tumor assessment at baseline
- Patient is evaluable for efficacy
- Patient had no CSR-reportable protocol deviations that may affect efficacy evaluation.

Patients will be evaluable for efficacy if they have at least one response assessed differently from ‘unknown’ or ‘not assessed’ as per RECIST v1.1. All CSR-reportable protocol deviations leading to exclusion from the PPS will be provided in a listing.

10.1.7 Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PAS) includes all patients who (a) receive the planned treatment, (b) provide at least one evaluable PK concentration, and (c) do not vomit within 4 hours after the dosing of BGJ398.

Detailed definition of PAS will be described in the statistical analysis plan (SAP). Patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples and whether the PK parameters can be reliably estimated based on the available blood samples. These patients will be identified at the time of the analyses.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be listed by patient and 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 and the relative dose intensity (computed as the ratio of actual cumulative dose and planned cumulative dose), will be listed and summarized by means of descriptive statistics.

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 by means of contingency tables.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with CSR-reportable protocol deviations. These will be identified prior to database lock and will be listed and summarized. Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions, see Section 10.5.2.6.

10.4 Primary objective

10.4.1 Variable

For Cohort 1, the primary objective of the study is to assess the efficacy of BGJ398 using overall response assessed by central imaging review.

Overall 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 RECIST version 1.1 (Appendix 3).

10.4.2 Statistical hypothesis, model, and method of analysis

It is assumed that the number of responses follow a binomial distribution.

The estimated ORR per central imaging review along with the 95% binomial exact CI will be provided.

10.4.3 Handling of missing values/censoring/discontinuations

Disposition including the reason for discontinuation from study treatment will be summarized and listed, along with dates of first and last study treatment, duration of exposure to BGJ398 and date of discontinuation for each patient.

Missing data will simply be noted as missing on appropriate listings.

The handling of censoring for time to event endpoints and completely/partial missing dates will be described in SAP.

10.5 Secondary objectives

This section describes analyses of secondary objectives for Cohort 1. The same variables will be analyzed for Cohorts 2 and 3 as exploratory, so this section also applies to analyses of those variables/endpoints (Section 3).

10.5.1 Secondary efficacy objectives and variables

Overall survival

Overall Survival (OS) is defined as the time from the date of start of treatment to the date of death due to any cause. The survival time for patients without documentation of death prior to the 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 at the date of start of treatment.

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

Progression Free Survival

Progression free survival (PFS) is defined as the date of the start of treatment to the date of the event defined as the first documented progression or death due to any cause. If patient has not had an event, progression- free-survival will be censored according to details described in the SAP. K-M analysis of PFS will be provided.

For Cohorts 2 and 3, the percentage of patients who are progression-free at the second scheduled scan (approximately 16 weeks from treatment initiation) or later will be analyzed using 95% exact binomial confidence interval. Patients who do not have scans to show that they are progression-free at the second scheduled scan or later will be considered as not benefiting from the study treatment. Sensitivity analysis will be done by estimating PFS >16 weeks using K-M estimate.

Overall Response Rate (ORR)

ORR (based on overall response assessed by the investigator) will be estimated with 95% binomial exact confidence interval.

Best Overall Response and Disease Control Rate

Overall lesion assessments will be listed by patient. Best overall response (BOR) will be summarized by the proportion of patients having a best overall response of PR, CR, SD, or PD. Disease control rate will be summarized presenting the combined proportion of patients having a BOR of CR, PR, or SD. The estimates will be presented along with corresponding 95% binomial exact confidence intervals. These analyses will be conducted for the central imaging assessment and for the investigator assessment as specified by cohort (Section 3).

10.5.2 Safety objectives and variables

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the safety analysis 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 90 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.

10.5.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to 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 treatment-emergent 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, relationship to study treatment.

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

Adverse events of special interest (AESI) will be considered. Each AESI consists of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified AESI, number and percentage of patients with at least one event within the AESI will be reported.

10.5.2.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version CTCAE v4.03, Grade 1 or higher will be assigned per CTCAE v4.03. 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 categorized as low/normal/high based on laboratory normal ranges.

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

- 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.

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

10.5.2.4 Other safety data

Data from other tests (eg, electrocardiogram, LVEF, or ophthalmic assessments) will be listed, notable values will be flagged. 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

- Table with frequency/percentage of patients with abnormal vital signs.

- Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.5.2.5 Supportive analyses for secondary objectives

Not applicable.

10.5.2.6 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 summarized. Categories for relative dose intensity of BGJ398 will be specified as ≤0.5, >0.5 - ≤0.75, >0.75 - ≤0.9, >0.9 - ≤1.0 and >1.0. The number and proportion of patients within each category will be presented.

10.5.3 Pharmacokinetics

Patients treated with FMI I and some patients treated with FMI III (sparse PK group) will have limited PK collected as indicated in Table 10. For these patients, only trough and 2-hr or 4-hr plasma concentration data will be available. No PK parameters can be calculated for these patients.

A secondary objective of this study is to characterize the single and multiple doses PK of BGJ398 FMI III and FMI IV formulations. Data as per Table 11 will be available for about 20 patients treated with FMI III and for all patients enrolled in either Cohort 2 or Cohort 3 and treated with FMI IV. For these patients, PK parameters as listed in Table 13, may be determined from PK profiles after the first dose on Day 1 of Cycle 1 and Day 15 of Cycle 1 after repeated daily dosing using non-compartmental method(s) of WinNonlin (Pharsight, Mountain View, CA).

Table 13: Non-compartmental pharmacokinetic parameters

Term	Definition
C_{max}	Maximum observed plasma concentration after drug administration [mass x volume^{-1}]
C_{trough}	Measured concentration at the end of a dosing interval (taken directly before next administration) [mass x volume^{-1}]
T_{max}	Time to reach C_{max} [time]
AUC_{24}	Area under the concentration-time curve from 0 to 24 hours [mass x time x volume^{-1}]
$T_{1/2}$	Elimination half-life associated with the terminal slope (lambda_z) of a semi-logarithmic concentration-time curve [time]
AUC_{inf}	Area under the concentration-time curve from 0 to infinity [mass x time x volume^{-1}]
CL/F	Apparent clearance [dose/AUC]
Vz/F	Apparent volume of distribution [dose/AUC x lambda_z]
R_{acc}	Accumulation ratio calculated as AUC_{0-24} of C1D15/AUC_{0-24} of C1D1 and C_{max} of C1D15/C_{max} of C1D1

10.5.3.1 Data handling principles

All concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics.

10.5.3.2 Data analysis principles

Exploratory PK analysis may be conducted based on preliminary data prior to data base lock, and nominal time and dose information may be used.

PK data generated from this study may be used in conjunction with PK data from other clinical studies for population PK and PK/PD assessment. These assessments will be reported separately. If possible, exploratory comparisons will be made to historical pharmacokinetic data. Available PK data from this study may be modeled using a population pharmacokinetic data analysis approach in order to characterize the population pharmacokinetics of BGJ398. Any population PK data generated will be reported separate from the CSR. If feasible, exploratory PK and PK/PD analysis may be performed, using appropriate methods, to elucidate concentration-response (efficacy and/or biomarkers) and/or concentration-toxicity relationships. These analyses will be defined in a stand-alone analysis plan document(s), as appropriate, prior to clinical database lock.

Descriptive graphical plots of individual and mean plasma concentration (per treatment) along with its time course will be generated. Further graphical exploratory analysis will be carried out if deemed appropriate.

Analysis will be done separately for the 3 formulations. In addition, analyses that require derived PK parameters will be applicable to patients treated with FMI III and FMI IV who are expected to provide extensive PK blood samples as indicated in Table 11.

10.5.3.2.1 Analysis sets

Only PK blood samples with the date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. Samples taken from patients who vomited within 4 hours of dosing will be excluded from the analysis. The PAS will be used.

10.5.3.2.2 Basic tables, Figures and Listings

The PK concentration and PK (when available for patients treated with FMI III or FMI IV), will be summarized and listed using relevant statistics by formulation, and study day. Descriptive statistics (mean, SD, CV% or median [range]) will be presented. When a geometric mean is presented, it will be stated as such. Only median values and ranges will be presented for T_{max}.

Graphical plots of individual and mean plasma concentration-time data will be generated for BGJ398 and its metabolites. This graphical presentation will be applicable to patients who are treated with FMI III or FMI IV and have PK profile collected as per Table 11.

Median, minimum and maximum will be calculated based on collected samples. All analyses will refer to BGJ398 and its metabolites. BGJ398 and its metabolites concentration vs time data will be reported. Exploratory PK analysis may be conducted based on preliminary data prior to data base lock and nominal time and dose information may be used.

10.5.4 Resource utilization

Not applicable.

10.5.5 Patient-reported outcomes

Not applicable.

10.6 Exploratory objectives

The details of the statistical analyses described in this section or any additional statistical analyses for the exploratory objectives may be a stand-alone analysis plan document, as appropriate. The results from the analyses, if conducted, may be reported separate from the CSR.

10.6.1 Biomarkers

DNA sequencing will be performed in order to detect changes from baseline in molecular and proteomic profiles in tumor tissue from patients who have progressed through treatment with BGJ398 using available paired biopsies.

Genetic alterations data will be available from the analysis of cell free tumor DNA and will be summarized and will be used for concordance analysis of baseline data and correlation analysis with markers with response and/or resistance.

10.6.1.1 Outline of the data analysis

PD markers collected in the clinical database will be analyzed by QED Therapeutics or designated CRO. Since this clinical trial was not designed to address specific hypotheses related to patient pre-selection or PD markers, the analysis of this data should be viewed as exploratory and hypotheses generating. Analytical results from such analyses may be used to generate additional hypotheses that must then be verified with data derived from subsequent clinical trials. No adjustment for multiple comparisons is planned.

If the number of samples is inadequate to perform a rigorous data analysis, then the available data will only be listed. Additional analyses that may be performed after the completion of the end-of-study clinical study report will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of patient pre-selection or PD markers generated from samples collected during the study but analyzed after the database lock and completion of the clinical study report.

10.6.1.2 Data handling principles

All measurements below their respective LLOQs or missing data will be labeled as such in the concentration data listings. Measurements below the LLOQ will be treated as zero in summary statistics. Change from baseline analyses will only be performed on patients with measurable samples and pre- and post-treatment time points.

10.6.1.3 Data analysis principles

10.6.1.3.1 Analysis sets

The FAS will be used for all analyses unless otherwise specified. The number of patients with measurable samples will be identified in the summaries and relevant proportions will be calculated against this number of patients.

10.6.1.3.2 Basic tables, figures and listings

Change from baseline for markers measured pre and post baseline to assess the effect on FGFR pathway will be listed by patient and may be summarized by means of descriptive statistics.

Correlation of baseline amplification status of FGFR or mutation status and clinical antitumor activity outcome will be summarized and may be explored graphically.

Individual CA19-9 serum levels (or change from baseline) will be listed as well as presented as line plots over time. If enough data is available, statistical analysis will be performed in order to assess the relationship between anti-tumor activity (BOR and OS) and CA19-9 levels (or change from baseline).

Patient's FGFR2 gene fusion status in DNA from non-tumor tissue (cell free DNA data) will be listed and compared to the FGFR2 gene fusion status in tumor tissue at baseline; a contingency table will be presented. Genetic alterations detected in cell free tumor DNA will be summarized and presented graphically for patients with both baseline and post-baseline samples. If there is enough data, change from baseline expression levels will be correlated with efficacy data. Further exploratory analyses will be performed if feasible.

10.6.1.3.3 Advanced analysis methods

Any advance analyses e.g. to assess potential correlation between baseline molecular status and clinical response, will be defined in a stand-alone analysis plan document, as appropriate.

10.6.2 Objectives for Cohorts 2 and 3

The variables for the exploratory objectives for Cohorts 2 and 3 are defined and analyzed as described in the previous sections, as applicable.

10.7 Interim analysis

Safety and efficacy data will be continuously monitored by QED Therapeutics in conjunction with the investigators for decision-making purposes. Please refer to Section 4.2 on the timing of the interim analysis.

Specifically, two formal interim analyses are planned for Cohort 1 after amendment 3:

- The first formal interim analysis for Cohort 1 was conducted when all patients in the Interim Efficacy Analysis Set 1 had been followed for at least 10 months after their initial exposure to BGJ398. Primary efficacy analyses were conducted for the Interim Efficacy Analysis Set 1, and key efficacy analyses were repeated for the Full Analysis Set. Safety analyses were conducted on the Full Analysis Set.

- The second formal interim analysis for Cohort 1 is planned when all patients who received BGJ398 at the time of the first formal interim analysis after amendment 3 have at least 10 months follow-up after their initial exposure to BGJ398. For this interim analysis, the primary analyses will be conducted on the Interim Analysis Set 2 for Cohort 1. The Sensitivity Analysis Set for Cohort 1 will be used for supportive sensitivity analyses.

For Cohort 3, a formal interim analysis will be conducted when the first dosed 10 patients in Cohort 3 have the potential to complete the second scheduled scan. This is to determine if an additional 10 patients will be added to Cohort 3.

10.8 Sample size calculation

10.8.1 Cohort 1

At the time of the first formal interim analysis after amendment 3, the Interim Efficacy Analysis Set 1 will include 72 patients with FGFR2 gene fusions or translocations. The half-width of the exact 95% confidence interval for ORR will not exceed 12%.

With at least 106 patients with FGFR2 gene fusions or translocations, the half-width of the exact 95% confidence interval width of ORR will not exceed 10%.

10.8.2 Cohorts 2 and 3

In Cohorts 2 and 3, patients who are progression-free at the second scheduled scan (approximately 16 weeks from treatment initiation) or later will be considered to be benefiting from study treatment. If the lower bound of the patients who are progression-free at the second scheduled scan (approximately 16 weeks) or later excludes 20%, the treatment will be considered as benefiting the patients.

For Cohort 2, the percentage of patients who are progression-free at the second scheduled scan (approximately 16 weeks) or later will be estimated with 95% exact confidence interval. There will be approximately 20 patients in total. A sample size of 20 will result in the exact 95% confidence interval half width of less than 23%. Patients who withdraw from the study for any reason before the second scheduled scan will be considered as not benefiting from study treatment. Sensitivity analysis will be conducted using the K-M method to estimate PFS >16 weeks.

Table 14 provides some examples of CIs corresponding to observed numbers of patients considered to have benefited from treatment. For example, if 9 of 20 patients are progression-free at the second scheduled scan or later, then the lower bound of the 95% exact confidence interval (CI) will exclude 20%.

In Cohort 3, the same definition of benefit rate as for Cohort 2 (the percentage of patients who are progression-free at the second scheduled scan [approximately 16 weeks] or later) will be applied. The benefit rate will be estimated with 95% exact confidence interval. The planned enrollment for Cohort 3 is a maximum of 20 patients. With 20 patients, the exact 95% confidence interval half width is <23%. One interim analysis is planned when 10 patients have been dosed and have the potential to be followed up for response for at least 2 scheduled scans. If at the interim analysis, ≥4 patients are progression-free at the second scheduled scan (after approximately 16 weeks) or later, the cohort will continue to enroll the additional 10 patients; otherwise, enrollment will stop at 10 patients. If ≤20% patients are benefiting from the study treatment, there is <12.1% chance that the decision after the interim analysis will lead to continuing enrollment.

The percentage of patients considered to have benefited from treatment will be estimated with 95% exact binomial CI. If all 20 patients are enrolled, the exact 95% CI half width will not exceed 23%. Table 14 provides some examples of CIs corresponding to observed numbers of patients considered to have benefited from treatment. At the final analysis, if 9 of 20 patients who are progression-free at the second scheduled scan or later, the lower bound of the 95% exact CI will exclude 20%.

Table 14: 95% CI examples corresponding to observed numbers of patients considered to have benefited from treatment (Cohorts 2 and 3)

Number of patients considered to have benefited from treatment	95% Exact CI
4	(0.057, 0.437)
8	(0.191, 0.640)
9	(0.231, 0.685)
10	(0.272, 0.728)
12	(0.361, 0.809)

CI: confidence interval; PFS: progression-free survival

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 QED Therapeutics monitors, auditors, QED Therapeutics Clinical Quality Assurance representatives, designated agents of QED Therapeutics, 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). Study patients will be informed in writing and orally before the start of the study about the nature and scope of the planned study procedures, in particular about the possible benefits and risks of participating in the study. Consent will be documented by signature on the ICF. The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their CRFs.

QED Therapeutics 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 E6 guideline, regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by QED Therapeutics before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the QED Therapeutics 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

QED Therapeutics 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 Publication of study protocol and results

QED Therapeutics 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.

11.5 Publication of study protocol and results

QED Therapeutics is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. QED Therapeutics assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials will be posted publically per local regulations.

QED Therapeutics follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted Authors will not receive remuneration for their writing of a publication, either directly from QED Therapeutics or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, QED Therapeutics supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

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 QED Therapeutics-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. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper 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 Sponsor 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 pseudonymization of the patients by replacing names with the study-specific subject identification number; patients must not be identified by names in any documents submitted to QED Therapeutics. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site. The names of study patients and all other confidential information are subject to medical confidentiality and the provisions of the General Data Protection Regulation (GDPR) and other applicable regulations or laws. Patient data may only be passed on in pseudonymized form beyond the study center. Third parties do not have access to original documents.

11.8 Audits and inspections

Source data/documents must be available for inspection by QED Therapeutics 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 QED Therapeutics 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 QED Therapeutics 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 QED Therapeutics, 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, QED Therapeutics should be notified of this action and the IRB/IEC at the 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 in Table 15 are based on the Indiana University School of Medicine's "Clinically Relevant" Table (Flockhart Table™; Flockhart 2007) and supplemented with the FDA Draft guidance and the online database Drugbank.ca. Note: this may not be an exhaustive list of medications, investigator should use this list as a guide.

Table 15: Drugs to be used with caution while on study

Category	Drug Names
CYP3A substrates with narrow therapeutic index	alfentanil, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, sirolimus, tacrolimus, terfenadine, warfarin sodium or any other coumadin-derivative anticoagulants, direct thrombin inhibitors (eg, argatroban), and Factor Xa inhibitors (eg, rivaroxaban)
Moderate inhibitors of CYP3A4	amprenavir, aprepitant, atazanavir, cannabinoids, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, fosamprenavir, imatinib, metronidazole, Schisandra sphenanthera, sertraline, suboxone, tofisopam, verapamil, zafirlukast
Moderate inducers of CYP3A4	bosentan, cotrimoxazole, efavirenz, etravirine, ethosuximide, genistein, metyrapone, mexiletine, modafinil, nafcillin, talviraline, tipranavir
Medications which alter the pH of the GI tract [a,b]	antacids, H_2 antagonists (eg, ranitidine), proton-pump inhibitors (eg, omeprazole)
Medications that have possible risk of TdP/QT prolongation	alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, oxytocin, paliperidone, pasireotide, quetiapine, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tamoxifen, tizanidine, vardenafil, venlafaxine, ziprasidone
Medications that have conditional risk of TdP/QT prolongation	amitriptyline, amisulpride, ciprofloxacin, clomipramine, desipramine, diphenhydramine, doxepin, fluoxetine, galantamine, imipramine, nortriptyline, paroxetine, protriptyline, sertraline, solifenacin, trazodone, trimethoprim-sulfa, trimipramine

Category	Drug Names
Medications with established potential for QT prolongation or TdP	amiodarone, anagrelide, arsenic trioxide, astemizole (off US market), azithromycin, bepridil (off US market), chloroquine, chlorpromazine, cisapride (off US market), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US market), dronedarone, droperidol, erythromycin, escitalopram, flecainide, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off US market), mesoridazine (off US market), methadone, moxifloxacin, ondansetron, pentamidine, pimozide, probucol (off US market), procainamide (oral off US market), quinidine, sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), terfenadine (off US market), thioridazine, vandetanib
BCRP substrates	atorvastatin, irinotecan, methotrexate, rosuvastatin, simvastatin, sulfasalazine, topotecan

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome p; FDA, Food and Drug Administration; GI, gastrointestinal; TdP, Torsades de Pointes
[a] BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.
[b] If possible, proton pump inhibitors should be avoided due to their long pharmacodynamic effect and replaced with H_2 antagonists or antacids.
Sources: FDA Guidance for Industry, 2017; Flockhart 2007; drugbank.ca.

14.2 Appendix 2: List of prohibited medications

Table 16: List of prohibited medications and substances while on study

Category	Drug name
Strong inhibitors of CYP3A4	clarithromycin, conivaptan, fluconazole, fluvoxamine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, norfloxacin, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits
Strong inducers of CYP3A4	avasimibe, carbamazepine, nevirapine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, St. John's wort, troglitazone
Medications which increase serum phosphorus and/or calcium	calcium, parathyroid hormone, phosphate, vitamin D (including multivitamins containing vitamin D)

14.3 Appendix 3: Guidelines for assessments of response

14.3.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse 2000) and the revised RECIST 1.1 guidelines (Eisenhauer 2009).

14.3.2 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.

- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.

- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts (ie, spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions eg, blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.3.3 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v.) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during followup. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow-up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the QED Therapeutics calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

    - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

    - No FDG-PET at baseline with a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).

- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- **Ultrasound**: When the primary endpoint of the study is overall response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (ie, after treatment to differentiate between residual benign

lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (ie, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.3.4 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.3.2.

- **Nodal target**: See Section 14.3.9.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.3.5 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 17) and non-target lesions (Table 18) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 19) as well as the presence or absence of new lesions.

14.3.6 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore, all such data applicable to a particular visit should be associated with the same assessment number.

14.3.7 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial “partial volume” effects (ie, size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (eg, borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.3.8 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a “non-zero size” will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice

thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

14.3.9 Determination of target lesion response

Table 17: Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.[2]
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1] SOD for CR may not be zero when nodal lesions are part of target lesions
[2] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3] Methodology change; See Section 14.3.4.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (ie, the “0 mm” recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease

- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 17 above (ie, a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.

- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.

- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.

- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.

- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.

- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
    - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
    - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
    - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

14.3.10 Determination of non-target lesion response

Table 18: Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1] Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**NonCR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).

- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest

"increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.3.10 (Determination of target lesion response) for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.3.11 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.3.13).

- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.3.4.

14.3.12 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 19.

Table 19: Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD	No	PR[2]
CR	UNK	No	PR
PR	Non-PD and not UNK	No	PR[1, 2]
SD	Non-PD and not UNK	No	SD[1]
UNK	Non-PD	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2] Unconfirmed PR will be considered SD for analysis purposes. If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.4 Appendix 4: FGFR1/2/3 Allowed Mutations (Known Activating Mutations)

Patients who have a mutation listed below meet the inclusion criterion 2c.

FGFR Mutation	Functional Effect
FGFR1 N546K	Activating
FGFR1 K656E	Activating
FGFR2 S252W	Activating
FGFR2 P253R	Activating
FGFR2 A315T	Activating
FGFR2 Y375C	Activating
FGFR2 C382R	Activating
FGFR2 N549K	Activating
FGFR2 K659E	Activating
FGFR3 R248C	Activating
FGFR3 S249C	Activating
FGFR3 G370C	Activating
FGFR3 S371C	Activating
FGFR3 Y373C	Activating
FGFR3 G380R	Activating
FGFR3 K650E	Activating
FGFR3 K650M	Activating

Sources: Helsten 2015, data on file.

14.5 Appendix 5: List of Highly Effective Methods of Contraception

The following is from the Clinical Trials Facilitation Group 2014 (Section 4.1).

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
  - oral
  - injectable
  - implantable [2]
- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS) [2]
- bilateral tubal occlusion [2]
- vasectomised partner [2,3]
- sexual abstinence [4]

1 Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see Clinical Trials Facilitation Group 2014, section 4.3).

2 Contraception methods that in the context of this guidance are considered to have low user dependency.

3 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.