Infigratinib (BGJ398)
Abbreviated Clinical Study Report CBGJ398X2204:
Final Analysis

1. TITLE PAGE

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

Indication:	Cholangiocarcinoma (second- or later-line)
Phase of Development:	2
First Subject Treated:	23 July 2014
Last Subject Completed:	07 February 2022
Date of Report:	30 January 2023
Coordinating Investigator:	Milind Javle, MD, University of Texas/ MD Anderson Cancer Center
Sponsor's Responsible Medical Officer:	David van Veenhuyzen, MBChB, MPharmMed
Study Medical Monitor:	David van Veenhuyzen, MBChB, MPharmMed
Sponsor:	QED Therapeutics, Inc. 1800 Owens Street, Suite C-1200 San Francisco, CA 94158
EudraCT Number:	2013-005085-19
Clinical Trials Identifier:	NCT02150967

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline, including the archiving of essential documents.

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
QED Therapeutics, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume: NA
Page: NA</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Investigational Product: Infigratinib (formerly BGJ398, also known as BBP-831 and infigratinib phosphate)</td></tr>
<tr><td>Name of Active Ingredient:
Infigratinib</td></tr>
<tr><td colspan="3">Title of Study: 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</td></tr>
<tr><td colspan="3">Coordinating Investigator: Milind Javle, MD, University of Texas/MD Anderson Cancer Center</td></tr>
<tr><td colspan="3">Study Centers: Subjects were enrolled across 22 study centers (9 in the United States, 5 in Western Europe, 6 in Asia, and 2 in the United Kingdom).</td></tr>
<tr><td colspan="2">Publication (reference): Javle 2018a, Javle 2018b</td><td></td></tr>
<tr><td colspan="2">Study and Reporting period:
Date first subject treated: 23 July 2014
Date of data cutoff for the primary analysis: 01 March 2021
Last patient, last visit for the study: 07 February 2022</td><td>Phase of development: 2</td></tr>
<tr><td colspan="3">Background and Rationale for the Study:
Cholangiocarcinoma is a serious and life-threatening disease with very limited treatment options and an overall poor prognosis. Standard of care first-line treatment of advanced or metastatic cholangiocarcinoma has a median survival of <1 year. For cholangiocarcinoma patients who relapse after first-line therapy, there is a need for more effective therapies with no established second-line standard of care. Nonclinical data and preliminary clinical evidence from Phase 1 and Phase 2 studies demonstrate the potential for infigratinib to treat serious and life-threatening disease in a refractory population. Infigratinib has a predictable, acceptable, and manageable on-target safety profile in subjects with malignancies.</td></tr>
<tr><td colspan="3">Overview of Study Cohorts (as of protocol version 06 [protocol amendment 5]):
Cohort 1: Subjects with fibroblast growth factor receptor 2 (FGFR2) gene fusions (ie, fusions or rearrangements [formerly translocations]; hereafter referred to as “FGFR2 fusions”) (excluded subjects with prior or current treatment with a selective FGFR inhibitor or mitogen-activated protein kinase [MEK] inhibitor therapy).
Cohort 2: Subjects with one of the following (excluded subjects with prior or current treatment with a selective FGFR inhibitor or MEK inhibitor therapy):
FGFR1 gene fusions.
FGFR3 gene fusions.
FGFR1/2/3 mutation known to be an activating mutation as noted in the study protocol [Appendix 16.1.1] (for mutations not listed in Appendix 4 of the protocol, enrollment could be allowed with written pre-approval of the QED medical monitor).</td></tr>
</table>

Of note, 12 subjects with other FGFR alterations (ie, nonfusion) were enrolled (ie, permitted by the protocol) to Cohort 1 before protocol amendment 2 was implemented, and 2 additional subjects were enrolled to Cohort 1 under permission by the sponsor (Novartis) after implementation of amendment 2. For purposes of this final analysis, results from these 14 subjects were combined with results from subjects in Cohort 2 (subjects with other FGFR alterations) and are hereafter collectively referred to as Cohort 2.

Cohort 3: Subjects with FGFR2 fusions who received prior treatment with a FGFR inhibitor other than infigratinib.

Objectives:

Primary: To evaluate the efficacy of single agent infigratinib in subjects with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or other FGFR genetic alterations in Cohort 1.

Secondary:

- To further evaluate the efficacy of single agent infigratinib (Cohort 1).
- To characterize the safety and tolerability of single agent infigratinib (Cohort 1).
- To determine selected trough and 2-hour or 4-hour plasma concentrations of infigratinib and its metabolites (overall study).
- To characterize the pharmacokinetic (PK) profile of infigratinib final market image (FMI) III and FMI IV formulations (overall study).

Exploratory:

- To characterize the safety and tolerability of infigratinib in subjects with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations other than FGFR2 fusions (Cohort 2) or with FGFR2 fusions who had received prior FGFR inhibitors other than infigratinib (Cohort 3).
- To evaluate the efficacy of single agent infigratinib in subjects with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations other than FGFR2 fusions (Cohort 2) or with FGFR2 fusions who had received prior FGFR inhibitors other than infigratinib (Cohort 3).
- To assess markers that may correlate with genetic alterations in tumor tissue at baseline, predictions of response and/or resistance (eg, gene mutations, amplifications, deletion and/or altered protein expression or activation) (overall study).

Endpoints:

Primary: Overall response in Cohort 1 assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Secondary:

- Overall response assessed by investigator; progression-free survival (PFS), best overall response (BOR), disease control assessed by investigator and by BICR according to RECIST version 1.1; and overall survival (OS) (Cohort 1).
- Safety (type, frequency, and severity of adverse events [AEs] and serious adverse events [SAEs]) and tolerability (dose interruptions, reductions, and intensity) (Cohort 1).
- Selected trough and 2-hour or 4-hour plasma concentration profiles and derived PK parameters of infigratinib and its metabolites (overall study).
- For FMI III and FMI IV: Plasma concentration profiles and derived PK parameters of FMI III and FMI IV (overall study).

Exploratory:

- Safety (type, frequency, and severity of AEs and SAEs) and tolerability (dose interruptions, reductions, and intensity) (Cohorts 2 and 3).
- PFS, overall response, BOR, response onset, and disease control assessed by the investigator per RECIST version 1.1, and OS (Cohorts 2 and 3).
- Deoxyribonucleic acid (DNA) sequencing of paired biopsies (tumor tissue) from subjects who progressed and analysis of cell free deoxyribonucleic acid (cfDNA) (overall study).
- Serial serum CA19-9 levels (overall study).

Methodology: This multicenter, open-label, 3-cohort, Phase 2 study evaluated infigratinib antitumor activity in subjects with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations. All subjects received oral infigratinib administered once daily for the first 3 weeks (21 days) of a 28-day treatment cycle. Study drug was continued until disease progression, unacceptable toxicity, withdrawal of treatment at the discretion of the investigator or of consent by the subject, lost to follow-up, or death. Once study drug was discontinued, subjects completed an End of Treatment (EOT) visit, followed by 30-day Safety Follow-up visit. Thereafter, subjects who discontinued study drug for any reason other than disease progression had tumor assessments every 8 weeks until disease progression or the initiation of subsequent antineoplastic therapies, or death, whichever occurred first. All subjects were followed for survival at least every 4 months after discontinuation of study drug. Survival follow-up was to continue for up to 5 years or until all subjects discontinued the study, died, withdrew consent, or were lost to follow-up. However, the study was terminated earlier than the full survival period due to sponsor decision.

Documented evidence of FGFR gene alterations was required for all subjects. The specific genetic alterations allowed were determined through molecular prescreening and subdivided into FGFR2 fusions vs other FGFR genetic alterations. After protocol amendment 2, enrollment into Cohort 1 was limited to subjects with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions. Protocol amendment 4 specified two additional cohorts: Cohort 2 and Cohort 3. Cohort 2 allowed for subjects with additional FGFR genetic alterations (other than FGFR2 fusions) and excluded subjects with prior or current FGFR inhibitor or MEK inhibitor therapy. Cohort 3 allowed for subjects with only FGFR2 fusions and required prior treatment with an FGFR inhibitor other than infigratinib.

The formulation of infigratinib was changed from FMI I to FMI III. Both of these formulations were taken by subjects in Cohort 1. PK, safety, and tolerability data from the first 20 subjects treated with FMI III up to the end of Cycle 1 were assessed and compared with the historical data from subjects treated with FMI I. Results of those analyses are provided in the primary CSR [X2204p].

Protocol amendment 4 specified that the FMI IV formulation be used for subjects in Cohorts 2 and 3. Additionally, subjects in Cohort 1 were transitioned to FMI IV when this formulation was available at the study center.

Number of subjects (planned and analyzed): Up to approximately 160 subjects were planned for enrollment, with approximately 120 subjects in Cohort 1, approximately 20 subjects in Cohort 2, and up to approximately 20 subjects in Cohort 3.

In total, 143 subjects were enrolled to the study and received at least 1 dose of study drug. Of these, 2 subjects (both in Cohort 2) were on study and were receiving infigratinib at the time of study termination. These subjects were transitioned to a patient access program (sponsored by Helsinn [Lugano, Switzerland]) in order to continue receiving infigratinib. All 143 subjects were included in the Full Analysis Set (FAS): 108 subjects in Cohort 1, 25 subjects in Cohort 2 (includes 14 subjects with other FGFR alterations enrolled into Cohort 1 prior to protocol amendment 2), and 10 subjects in Cohort 3.

Diagnosis and main criteria for inclusion: This study included adult subjects with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or other FGFR genetic alterations who failed or were intolerant to gemcitabine-based antineoplastic treatment.

Main inclusion criteria:

- Histologically or cytologically confirmed cholangiocarcinoma at the time of diagnosis. Subjects with cancers of the gallbladder or ampulla of Vater were not eligible.
- Written documentation of local or central laboratory determination of the following FGFR gene alterations from a sample collected before infigratinib treatment:
  - Cohort 1: FGFR2 fusions.
  - Cohort 2: one of the following: (a) FGFR1 fusions, (b) FGFR3 fusions, or (c) FGFR1/2/3 mutation known to be an activating mutation and noted in the protocol [Appendix 16.1.1] (protocol Appendix 4).
  - Cohort 3: FGFR2 fusions (must have received prior treatment with an FGFR2 inhibitor other than infigratinib).
- Evidence of measurable disease according to RECIST version 1.1.
- Receipt of at least one prior regimen containing gemcitabine with or without cisplatin. Subjects must have had evidence of progressive disease after their prior regimen; if prior treatment was discontinued due to toxicity, subjects must have had had continued evidence of measurable disease.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1 (subjects with ECOG PS of 2 could be considered on a case-by-case basis after discussion with QED Therapeutics).

Main exclusion criterion: Prior treatment with an FGFR2 inhibitor or MEK inhibitor was not allowed, with the exception of Cohort 3 (protocol amendment 4), which required prior FGFR2 inhibitor therapy.

Investigational product, dosage, and mode of administration; batch number(s): Subjects received oral infigratinib 125 mg once a day (QD) (administered as one 100-mg capsule and one 25-mg capsule) using a "3-weeks on, 1-week off" schedule for each 28-day treatment cycle.

Three formulations of infigratinib were used in the study: FMI I, FMI III, and FMI IV.

FMI III replaced FMI I after implementation of protocol amendment 2. With protocol amendment 4, the FMI IV formulation was used for subjects in Cohort 2 and 3. Additionally, subjects in Cohort 1 were transitioned to FMI IV when this formulation was available at the study center.

Batches of infigratinib were supplied from formulations FMI I, FMI III, and FMI IV, and batch numbers are provided in Appendix 16.1.6.

Duration of treatment: Study drug was to be continued until disease progression, unacceptable toxicity, withdrawal of treatment at the discretion of the investigator or of consent by the subject, lost to follow-up, or death. However, the study was terminated earlier due to sponsor decision.

Reference therapy, dosage, and mode of administration: none.

Criteria for evaluation:

This abbreviated CSR represents the final formal analysis of Study CBGJ398X2204 with focus on safety results.

Safety: The safety evaluation is based on tolerability of study treatment, AE reporting, laboratory parameters, pregnancy outcome (if applicable), ophthalmic assessments, 12-lead electrocardiograms (ECGs), cardiac imaging, vital signs, physical examinations, and ECOG PS. A separate report on cardiac

safety evaluation, including QTc/PK modeling, was also prepared using a separate cardiac safety analysis plan (this report is not included herein).

Statistical methods: The FAS included all subjects who received at least one dose of infigratinib. Unless otherwise specified, all analyses were done separately for each cohort.

The primary efficacy analysis for study CBGJ398X2204 is reported in the primary CSR [X2204p-Section 11.1]. After the primary efficacy analysis, there were no additional efficacy endpoints to assess for Cohort 1. Therefore, the final efficacy analysis for Cohort 1 is the same as that reported in the primary CSR. Efficacy data were not re-analyzed for this aCSR. For Cohort 2 and Cohort 3, only minimal efficacy was observed at an interim analysis (as permitted by the protocol). As a result, the sponsor terminated the study early. By-subject listings of efficacy endpoints and tumor responses for individual subjects are provided by cohort, however efficacy summary tables were not prepared. For reference, an overview of statistical methods supporting the efficacy analyses is provided below.

The primary efficacy analysis endpoint was overall response rate (ORR) in Cohort 1 only, assessed by BICR. Any confirmed complete response (CR) or partial response (PR) up to the data cutoff date for the primary CSR was considered as a responder for overall response, irrespective of when it occurred. The estimated ORR is presented with corresponding 95% CI based on the binomial distribution (Clopper-Pearson exact method) accompanied by duration of response (DOR) to allow for more complete characterization of the beneficial effect infigratinib may have. Secondary efficacy variables were evaluated using appropriate methods. Best overall response (BOR) was summarized separately for the rate of BOR of confirmed CR, confirmed PR, stable disease, and progressive disease; it was also summarized for disease control rate (the proportion of subjects having a BOR of confirmed CR or PR, or stable disease) and DOR. Kaplan-Meier (KM) analysis of PFS was provided. Similarly, OS was analyzed using the KM method. Survival rate at 4, 6, 8, 12, 18, and 24 months and median OS were estimated with 95% CIs. Estimates were presented along with corresponding 95% exact CIs. The concordance of BOR based on BICR and investigator assessment was also assessed.

The same secondary efficacy variables were analyzed and assessed using by-subject listings for Cohorts 2 and 3 as exploratory endpoints, so the approaches described above also apply.

For subjects who underwent extensive PK sampling, descriptive statistics were used to summarize drug concentrations and PK parameters. Graphical plots of individual and mean plasma concentration- time data were generated. Results of the PK analysis are provided in a separate PK report [QEDT-NCA-BGJ398-827-v5].

Standard safety presentations were prepared, including summaries of AEs of special interest.

RESULTS

This abbreviated CSR represents the final formal analysis of Study CBGJ398X2204 with focus on safety results for Cohorts 1, 2, and 3. No new efficacy analyses were conducted due to early termination of the study by the sponsor. Early study termination was not due to concerns about safety and had no impact on the primary efficacy analysis for the study. For full details on the efficacy of infigratinib, see the primary CSR [X2204p]. Results of the PK analysis are provided in a separate PK report [QEDT-NCA-BGJ398-827-v5].

Safety Results:

The median duration of exposure to infigratinib was longer for Cohort 1 (5.6 months), relative to Cohort 2 (2.33 months), and Cohort 3 (1.63 months). Across all cohorts, most subjects (>50%) were exposed to infigratinib for ≤6 months with very few subjects (primarily in Cohort 1) treated for >12 months. Median relative dose intensity was approximately 75% to 85% across cohorts.

The most common AE across all cohorts combined was hyperphosphatemia (range: 70.0% to 92.0%), followed by stomatitis (52.0% to 70.0%), and fatigue (30.0% to 40.7%). Other frequently reported events

for Cohort 1, which had the largest number of subjects, included alopecia (39.8%), dry eye (36.1%), palmar-plantar erythrodysesthesia syndrome (34.3%), arthralgia (32.4%), constipation (31.5%), and dysgeusia (31.5%).

Nine subjects died during the on-treatment period: 6 subjects (5.6%) in Cohort 1 and 3 (12.0%) in Cohort 2. Eight of the on-treatment deaths were due to the study indication (cholangiocarcinoma), and 1 subject in Cohort 2 died of intestinal ischemia. Of note, one additional subject (Cohort 1) had an on-treatment SAE (Grade 4 sepsis, not related to study treatment) that subsequently resulted in death after the treatment period.

Treatment-emergent SAEs occurred in 48 of 143 subjects (33.6%) in the study. Thirteen (9.1%) of these subjects had ≥ 1 treatment-related SAE. For subjects in Cohort 1, the most common SAEs (regardless of attribution to study drug) were anemia (3.7%), pyrexia (3.7%), hypercalcemia (3.7%), and sepsis (2.8%). In Cohort 2, SAEs were reported in 11 subjects (44.0%). Pyrexia was reported in 2 subjects. The other SAEs, reported in 1 subject each, were abdominal pain, arthralgia, bile duct stone, blood creatinine increased, GI hemorrhage, general physical health deterioration, hip fracture, hyponatremia, influenza, intestinal ischemia, muscular weakness, pain in extremity, pelvic pain, peripheral ischemia, pleural effusion, and sepsis. In Cohort 3, 5 SAEs (ascites, gastroesophageal reflux disease, hypophosphatemia, nausea, and vomiting) were reported in 2 subjects (20.0%). Overall, 25 subjects (17.5%) discontinued study drug due to an AE. None of the AEs led to treatment discontinuation in >2 subjects. A total of 94 (65.7%) subjects had an AE that led to dose interruption; 78 (54.5%) subjects had a dose adjustment/reduction due to an AE. Concomitant medication or non-drug therapy due to an AE was required in the majority (95.8%) of subjects.

Infigratinib at therapeutic doses is associated with disturbances in calcium phosphate homeostasis, based on nonclinical findings. Precautions taken in this study included exclusion of subjects with significant pre-existing ectopic calcifications and/or endocrine alteration of calcium phosphate homeostasis and exclusion of subjects with significant pre-existing cardio- and cerebrovascular disease who had evidence of vascular calcifications. Medications known to increase serum phosphate and calcium levels were restricted, and serum phosphate and calcium levels were closely monitored. Hyperphosphatemia was managed with a low phosphate diet and phosphate lowering therapy, as clinically indicated.

Hyperphosphatemia (PTs: hyperphosphatemia, increased blood phosphorus) occurred in 114 of 143 (80.0%) subjects (range: 70.0% to 92.0% across cohorts), and most events across all cohorts were deemed by the Investigator as related to infigratinib. There were no Grade 4 events of hyperphosphatemia reported in the study. In Cohort 1, 12.0% of subjects had Grade 3 hyperphosphatemia (of which 1 subject [0.9%] had a treatment-emergent SAE of hyperphosphatemia; no subjects discontinued study drug due to the event). Hyperphosphatemia was asymptomatic and was the most common AE that led to dose interruption (25.9%), dose reduction (27.8%), or required concomitant medication or non-drug therapy (66.7%). Hyperphosphatemia had a median onset of 8 days and resolved in most subjects. In Cohort 2, 2 subjects (8.0%) had Grade 3 hyperphosphatemia, 5 subjects (20.0%) had events that led to dose interruption, 3 subjects (12.0%) had events that led to dose reduction, and 18 subjects (72.0%) required concomitant medication or non-drug therapy for the event. In Cohort 3, 2 subjects (20.0%) had Grade 3 hyperphosphatemia, 1 subject (10.0%) discontinued treatment due to the event, 2 subjects (20.0%) had their dose interrupted, 1 subject (10.0%) had the dose reduced, and 6 subjects (60.0%) required concomitant medication or non-drug therapy for hyperphosphatemia.

Across the study, hypophosphatemia and hypercalcemia occurred in 32 subjects (22.4%) and in 35 subjects (24.5%), respectively; were mostly Grade 1 or 2 in severity and nonserious (though 1 subject in Cohort 3 had an SAE of hypophosphatemia); led to relatively few dose interruptions, reductions, and concomitant therapy; and did not lead to study drug discontinuation.

Due to the role of FGF/FGFR signaling on calcium/phosphate metabolism and in the maintenance of adult bone homeostasis, there is a mechanistic risk that infigratinib may increase the risk for fractures.

Pathological fractures (fractures considered due to the mechanism of action of infigratinib, without confounders or alternative etiologies) were observed in 3 subjects (2.1%) in this study.

In total, 91 subjects (63.6%) had an eye disorder (counted as an AESI except CSR/RPED), and 21 subjects (14.7%) had CSR/RPED.

AEs, ECGs, and LVEF measurements demonstrated no evidence to suggest that there is any deleterious effect of infigratinib on cardiac function. Cardiac AESIs were generally Grade 1 or Grade 2 in severity; none were Grade 4.

Two subjects (1.4%) had an AESI of acute pancreatitis (narrow search) for Grade 1 and Grade 2 pancreatitis, neither of which was considered to be related to infigratinib by the investigator. The Grade 2 event spontaneously resolved within 3 days of onset and the subject with the Grade 3 event was recovering. Four (2.8%) subjects had an AESI of tissue calcification, with one case of calciphylaxis (Peyronie's disease).

Assessment of AEs and laboratory measurements demonstrated no evidence of hepatic toxicity with infigratinib. Generally, Grade 3 and Grade 4 abnormalities in liver function tests were transient in nature or showed reversibility with dose interruption/reduction. In Cohort 1, 2 subjects (1.9%) had AST or ALT (AT) >3×ULN combined with TBL ≥2.0×ULN, concurrently on the same day, and no cholestasis (ie, ALP <2×ULN). While the drug-induced liver injury (DILI) assessment is never definitive, analyses of all factors involved for these 2 subjects indicate that there were no cases of DILI in this study. In Cohort 2, 3 subjects (12.0%) had at least 1 occurrence of AT >3×ULN combined with TBL ≥2.0×ULN concurrently on the same day. In Cohort 3, there were no occurrences of AT ≥3×ULN and TBL ≥2×ULN. There were no cases of DILI in either Cohort 1 or Cohort 3.

CONCLUSIONS

This abbreviated CSR represents the final formal analysis of Study CBGJ398X2204 with focus on safety results as no new efficacy analyses were conducted.

The overall safety profile of infigratinib reflects on-target effects and appears consistent with other FGFR tyrosine kinase inhibitors and drugs with a similar mechanism of action as well as expected AEs for oncology patients, many of whom had late-stage disease and/or were heavily pretreated. These safety results are consistent with the predictable and manageable safety profile observed for subjects enrolled in CBGJ398X2204 in previous data snapshots, as well as the safety profile observed across all studies with infigratinib. Safety risks can be managed with monitoring of clinical laboratory values, periodic eye examinations, concomitant therapy, and dose interruptions or modifications.

Date of Report: 30 January 2023