Infigratinib (BGJ398)
Abbreviated Clinical Study Report QBGJ398-301: Final Analysis

TITLE PAGE

A Phase 3 Multicenter, Open-Label, Randomized, Controlled Study of Oral Infigratinib Versus Gemcitabine with Cisplatin in Subjects With Advanced/Metastatic or Inoperable Cholangiocarcinoma With FGFR2 Gene Fusions/Translocations: the PROOF Trial

Indication:	Cholangiocarcinoma (second- or later-line)
Phase of Development:	3
First Subject Treated:	02 January 2020
Last Subject Completed:	02 March 2023
Date of Report:	06 September 2023
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:	2018-004004-19
Clinical Trials Identifier:	NCT03773302

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.

SYNOPSIS

Name of Sponsor/Company: QED Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier Volume: NA Page: NA	*(For National Authority Use Only)*
Name of Investigational Product: Infigratinib (formerly BGJ398, also known as BBP-831 and infigratinib phosphate)		
Name of Active Ingredient: Infigratinib		

Title of Study: A Phase 3 multicenter, open-label, randomized, controlled study of oral infigratinib versus gemcitabine with cisplatin in subjects with advanced/metastatic or inoperable cholangiocarcinoma with FGFR2 gene fusions/translocations: the PROOF Trial

Study Centers: Subjects were enrolled across 38 study centers (15 in Western Europe, 16 in North America, and 7 in Asia).

Publication (reference): None.	
Study and Reporting period: Date first subject treated: 02 January 2020 Last patient completed: 02 March 2023 (Study terminated early)	**Phase of development:** 3

Background and Rationale for the Study:

Cholangiocarcinoma (CCA) is a serious and life-threatening disease with very limited treatment options and an overall poor prognosis. Gemcitabine with cisplatin (gemcitabine/cisplatin) has been established as the standard of care for first line treatment in patients with advanced or metastatic CCA. Still, the median progression-free survival (PFS) was 8.0 months and median overall survival (OS) was 11.7 months. Study CBGJ398X2204 suggested that infigratinib could offer a targeted, chemotherapy-free therapeutic option for first line treatment in patients with advanced or metastatic CCA with FGFR2 fusions. A growing understanding of the genetic alterations involved in the tumorigenesis of CCA provides new therapeutic options for molecular targets. Among other genetic alterations, recurrent fusions involving the fibroblast growth factor receptors (FGFRs) have been identified as an important class of driver mutations in a number of tumor types, including CCA (Wu 2013, Arai 2014, Jiao 2013). The FGFR family of receptors (FGFR1-4) serve as the high-affinity receptors for 22 FGF ligands. These are pleiotropic growth factors that control cell proliferation, migration, angiogenesis, apoptosis, and differentiation and are involved in both developmental and adult tissue homeostasis. In addition to CCA, FGFR2 fusions with different partners have been detected in bladder, thyroid, prostate, pancreatic, breast, lung, glioma, and other cancer types (Parker 2014; Wu 2013; Helsten 2016; Babina 2017).

Infigratinib is an orally bioavailable, potent, and selective ATP-competitive inhibitor of FGFRs 1-3, which has demonstrated anti-tumor activity in nonclinical in vitro and in vivo tumor models harboring FGFR genetic alterations. In Phase 1 and Phase 2 studies, evidence of clinical activity and a predictable, acceptable, and manageable on-target safety profile have been observed in adult patients with unresectable locally advanced or metastatic CCA demonstrating the potential for infigratinib to treat a population with serious, life-threatening, refractory disease.

The purpose of this study is to evaluate the efficacy of infigratinib, relative to the standard of care (gemcitabine/cisplatin), in subjects with advanced/metastatic or inoperable CCA harboring FGFR2 gene fusions/translocations.

Overview of Study Design (as of Protocol Amendment 4.0):

Study QBGJ398-301 (the PROOF trial) was a multicenter, open label, randomized, controlled Phase 3 study to determine if treatment with infigratinib improves PFS assessed by blinded independent central review (BICR) (primary objective) and OS (key secondary objective) compared to treatment with gemcitabine and cisplatin in subjects with advanced/metastatic or inoperable CCA with FGFR2 fusion/rearrangement.

Subjects were randomized in a 2:1 ratio to the following groups:

- Cohort 1: infigratinib 125 mg, administered once daily for the first 3 weeks (21 days) of a 28-day treatment cycle
- Cohort 2: gemcitabine/cisplatin administered by IV infusion on Days 1 and 8 of a 21-day treatment cycle.

During the treatment period, subjects were radiographically evaluated every 8 weeks±7 days from the first dose of study drug, regardless of drug interruption, for tumor response using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Treatment in each group continued until radiographic progressive disease confirmed by BICR, unacceptable toxicity, or other reason for discontinuation as permitted by the protocol (see Appendix 16.1.1). Subjects randomized to the gemcitabine/cisplatin group may have been eligible to cross over and receive infigratinib if radiographic progressive disease confirmed by BICR was observed. Subjects who crossed over to infigratinib continued on treatment until a criterion to discontinue treatment was met.

Objectives:

Primary: To determine if treatment with infigratinib improves PFS as assessed by BICR compared to treatment with gemcitabine and cisplatin in subjects with advanced/metastatic or inoperable CCAwith FGFR2 fusion/rearrangement.

Secondary:

- To determine if treatment with infigratinib improves OS compared to treatment with gemcitabine and cisplatin in subjects with advanced/metastatic or inoperable CCA with FGFR2 fusion/rearrangement.
- To evaluate the efficacy of infigratinib treatment compared to gemcitabine and cisplatin in terms of investigator assessed PFS.
- To further evaluate the efficacy in subjects treated with infigratinib versus gemcitabine and cisplatin by overall response rate (ORR), best overall response (BOR), duration of response (DOR), and disease control rate (DCR) determined by BICR and by the investigator.
- To characterize the safety and tolerability of single agent infigratinib.

Exploratory: A number of Exploratory objectives were included in the protocol, however, due to early termination of the study, they were not evaluated.

Endpoints:

Primary: PFS (from date of randomization until date of progression as determined by BICR or death due to any cause, whichever is earlier).

Secondary:

- OS (from date of randomization until date of death)
- PFS as determined by the investigator
- ORR assessed by BICR according to RECIST Version 1.1
- ORR assessed by the investigator according to RECIST Version 1.1
- BOR, DCR (partial response [PR + complete response [CR] + stable disease, and DOR (only for subjects who have a response) assessed by BICR and by the investigator according to RECIST 1.1
- Type, frequency, and severity of adverse events (AEs) and serious AEs (SAEs), laboratory abnormalities, and other safety findings.

Exploratory: A number of Exploratory objectives were included in the protocol, however, due to early termination of the study, they were not evaluated.

Methodology:

This was a multicenter, open label, randomized, controlled Phase 3 study to determine if treatment with infigratinib improves PFS assessed by BICR (primary objective), and OS (key secondary objective) compared to treatment with gemcitabine and cisplatin in subjects with advanced/metastatic or inoperable CCAwith FGFR2 fusion/rearrangement.

Subjects were randomized in a 2:1 ratio to receive oral infigratinib 125 mg administered once a day (QD) for the first 3 weeks (21 days) of a 28-day treatment cycle or to a regimen of gemcitabine (1000 mg/m^2) with cisplatin (25 mg/m^2) administered by IV infusion on Days 1 and 8 of a 21-day treatment cycle. Randomization was stratified by unresectable locally advanced vs metastatic disease, geographic region (North America, Western Europe, Asia Pacific, and rest of the world), prior neoadjuvant/adjuvant treatment (yes/no) and received up to 1 cycle of prior gemcitabine-based chemotherapy for unresectable locally advanced or metastatic disease (yes/no).

Treatment in each group continued until radiographic progressive disease confirmed by BICR, unacceptable toxicity, or other reason for discontinuation as permitted by the protocol (Appendix 16.1.1). Subjects randomized to the gemcitabine/cisplatin group may have been eligible to cross over and receive infigratinib if radiographic progressive disease confirmed by BICR was observed. Subjects who crossed over to infigratinib continued on treatment until a criterion to discontinue treatment was met (Appendix 16.1.1).

Once study drug was discontinued, subjects completed an End-of-Treatment (EOT) visit within 8 days of the decision to discontinue study drug, followed by a 30-day Safety Follow-up visit. Subjects who discontinued study drug for any reason other than disease progression had tumor assessments every 8 weeks until disease progression (even if subjects had started a new anticancer treatment). Subjects who discontinued study drug for disease progression were followed approximately every 3 months for survival status and new anticancer therapy information until the end of study (EOS). EOS was defined as the time when 224 OS events have been reached (for the primary OS analysis) and the last subject had completed study treatment. However, the study was terminated earlier than the full survival period due to sponsor decision. The decision to stop development of infigratinib in the oncology setting was not made based on any efficacy or safety concerns.

Number of subjects (planned and analyzed):

Approximately 300 subjects with a likely or known activating FGFR2 fusion/rearrangement determined by a central laboratory or local laboratory were planned for study participation. Note: Central laboratory determination of FGFR2 fusion/rearrangement was required for all subjects but local determination of FGFR2 fusion/rearrangement could be obtained and used for eligibility and randomization prior to central laboratory results being available. If available FGFR2 fusion/rearrangement determination was from the central laboratory being used in the study, a tumor sample did not need to be submitted for central FGFR2 fusion/rearrangement molecular testing.

In total, 48 subjects were enrolled into the study and received at least 1 dose of study drug. All 48 subjects were included in the safety analysis: 29 subjects in the infigratinib group and 19 in the gemcitabine/cisplatin group.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Had histologically or cytologically confirmed unresectable locally advanced or metastatic CCA. Subjects with gallbladder cancer or ampulla of Vater carcinoma were not eligible.
2. Had written documentation of local laboratory or central laboratory determination of a known or likely activating FGFR2 fusion/rearrangement from a sample collected before randomization. Note: All subjects enrolled based on local molecular test results must have had sufficient tumor tissue for confirmation of FGFR2 fusion/rearrangement by the central laboratory, but this central confirmation was not required prior to enrollment in the study.
3. Had an archival tumor tissue sample available with sufficient tumor content for FGFR2 fusion/rearrangement molecular testing by the central laboratory. However, if an archival tumor tissue sample was not available or did not meet requirements for central testing, a newly obtained (before randomization) tumor biopsy could be submitted instead. If prestudy written documentation of FGFR2 fusion/rearrangement in tumor tissue was available from the central laboratory, an additional tumor sample did not need to be submitted.
4. Had full recovery from the following permitted prior treatments (as applicable) such that the subject was reasonably expected to tolerate study treatment (gemcitabine/cisplatin or infigratinib) according to the investigator's assessment:
    a. A non-curative operation (ie, R2 resection [with macroscopic residual disease] or palliative bypass surgery only).
    b. Curative surgery with evidence of unresectable disease relapse requiring systemic chemotherapy.
    c. Adjuvant radiotherapy (with or without radio-sensitizing low-dose chemotherapy) for localized disease provided there had been clear evidence of disease progression before inclusion in the study.
    d. Adjuvant or neoadjuvant chemotherapy, provided recurrence occurred >6 months after the date of the last dose of adjuvant or neoadjuvant therapy and before randomization.
    e. Gemcitabine-based chemotherapy for advanced/unresectable or metastatic CCA (≤1 cycle):
        i. Recovery from acute toxicities to the extent that would allow initiation of cisplatin-gemcitabine (absolute neutrophil count (ANC) ≥1,000/mm^3 (≥1.0 × 10^9/L); platelets ≥100,000/mm^3 (≥100× 10^9/L).
        ii. Baseline tumor assessment at least 7 days after the last dose of chemotherapy and before randomization.
        iii. The window between the last dose of chemotherapy and the start of randomized study treatment had to be ≥14 days and ≤5 weeks.

f. Photodynamic treatment provided there was clear evidence of disease progression at the local site or at a new metastatic site.

5. Was ≥18 years of age of either gender.
6. Had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
7. Had a life expectancy >3 months.
8. Was able to read and/or understand the details of the study and provide written evidence of informed consent as approved by Institutional Review Board/Independent Ethics Committee (IRB/IEC).
9. Was able to swallow and retain oral medication.
10. Was willing and able to comply with scheduled visits, treatment plan and laboratory tests.
11. If a woman of childbearing potential (WOCBP), must have had a negative pregnancy test within 7 days of the first dose of study drug. A woman was not of childbearing potential if she had undergone surgical sterilization (total hysterectomy, bilateral tubal ligation or bilateral oophorectomy at least 6 weeks before taking study drug) or if she was postmenopausal and had 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 was no other cause of amenorrhea (eg, hormonal therapy, prior chemotherapy).

    WOCBP and males whose sexual partners are WOCBP must have agreed to use barrier contraception and a second form of highly effective contraception (Clinical Trials Facilitation Group 2014) while receiving study drug and for 1 month following their last dose of infigratinib or 6 months following their last dose of gemcitabine/cisplatin (or according to local labeling and standard institutional practice). Alternatively, total abstinence was also considered a highly effective contraception method when this was in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception.

    Sexually active males must have used a condom during intercourse while taking drug and for 1 month after the last dose of infigratinib or 6 months after the last dose of gemcitabine/cisplatin (or according to local labeling and standard institutional practice) and should not have fathered a child during this period. A condom was required to be used by vasectomized men and by men having intercourse with a male partner, to prevent delivery of the drug via seminal fluid.

Main exclusion criteria:

To be eligible for the study, subjects must not have met any of the following criteria:

1. Had received treatment with any systemic anticancer therapy for unresectable locally advanced or metastatic CCA, with the following exceptions:
    a. Prior neoadjuvant or adjuvant therapy was permitted if documented disease recurrence occurred ≥6 months after the last date of neoadjuvant or adjuvant therapy.
    b. One cycle of gemcitabine-based chemotherapy for locally advanced or metastatic CCA was permitted before randomization.
2. Had a history of a liver transplant.
3. Had previously or were currently receiving treatment with a mitogen-activated protein kinase (MEK) or selective FGFR inhibitor.
4. Had neurological symptoms related to underlying disease requiring increasing doses of corticosteroids. Note: Steroid use for management of central nervous system tumors was allowed but must have been at a stable or decreasing dose of corticosteroids for at least 2 weeks preceding randomization.

5. Had a history of another primary malignancy within 3 years except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin or any other curatively treated or surveilled malignancy (eg, localized low-risk prostate cancer) that was not expected to require treatment for recurrence during the course of the study.
6. Had any other medical condition that would, in the investigator's judgment, prevent the subject's participation in the clinical study due to safety concerns or compliance with clinical study procedures.
7. Had current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, inflammation, or ulceration, keratoconjunctivitis, or diabetic retinopathy, confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation could be enrolled in the study.
8. Had a 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.
9. Had impaired gastrointestinal (GI) function or GI disease that could have significantly altered the absorption of oral infigratinib (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome, small bowel resection).
10. Had current evidence of endocrine alterations of calcium/phosphate homeostasis (eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis).
11. Was currently receiving, or was planning to receive during the study, treatment with agents that are known moderate or strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Subjects were not permitted to receive enzyme-inducing anti-epileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone.
12. Had consumed 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 of study drug.
13. Had insufficient bone marrow function:
    a. Absolute neutrophil count (ANC) <1,000/mm^3 (1.0×10^9/L).
    b. Platelets <100,000/mm^3 (<100×10^9/L).
    c. Hemoglobin <8.5 g/dL; transfusion support was allowed if >1 week before randomization and hemoglobin remained stable.
14. Had insufficient hepatic and renal function:
    a. Total bilirubin >1.5 × upper limit of normal (ULN) (for patients with documented Gilbert syndrome, direct bilirubin ≤1.5 × ULN and enrollment required approval by the medical monitor).
    b. Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) >2.5 × ULN (AST and ALT >5 × ULN in the presence of liver involvement of CCA).
    c. Calculated (using the Cockcroft-Gault formula [Cockcroft 1976]) or measured creatinine clearance of <45 mL/min (or value ≥45 mL/min that excludes administration of cisplatin per local label and institutional guidelines).

15. Had amylase or lipase >2.0 × ULN.
16. Had elevated phosphorus or abnormal serum calcium, or calcium-phosphorus product ≥55 mg^2/dL^2:
    a. Inorganic phosphorus >1.1 × ULN.
    b. Total corrected serum calcium >11 mg/dL or <8 mg/dL.
17. Had clinically significant cardiac disease including any of the following:
    a. Congestive heart failure requiring treatment (New York Heart Association Grade ≥2B) or uncontrolled hypertension (refer to the European Society of Cardiology and European Society of Hypertension guidelines [Williams 2018]).
    b. Presence of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade ≥2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality.
    c. Unstable angina pectoris or acute myocardial infarction ≤3 months prior to first dose of study drug.
    d. QTc corrected by Fridericia's formula (QTcF) >470 msec (males and females). Note: If the QTcF was >470 msec in the first ECG, a total of 3 ECGs separated by at least 5 minutes was to be performed. If the average of these 3 consecutive results for QTcF was ≤470 msec, the subject met eligibility in this regard.
    e. Known history of congenital long QT syndrome.
18. Had had a recent (≤3 months prior to first dose of study drug) transient ischemic attack or stroke.
19. Had CTCAE (v5.0) Grade ≥2 hearing loss.
20. Had CTCAE (v5.0) Grade ≥2 neuropathy.
21. If female, was pregnant or nursing (lactating), where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or blood laboratory test.
22. Had known microsatellite instability-high (MSI-H) disease and the decision was made by the treating investigator that an alternative, non-study therapy was warranted according to standard of care.
23. Had any known hypersensitivity to gemcitabine, cisplatin, calcium-lowering agents, infigratinib, or their excipients.
24. Had any contraindication to cisplatin or gemcitabine treatment according to local labeling or standard institutional practice.
25. Had taken any Chinese herbal medicine or Chinese patent medicine treatments with anticancer activity within 14 days of the first dose of study drug.
26. Had received a live vaccine within 30 days before the first dose of study drug or was planning to receive a live vaccine during participation in this study.

Investigational product, dosage, and mode of administration: Infigratinib 125 mg (administered orally as one 100-mg capsule and one 25-mg capsule) once a day using a "3-weeks on, 1-week off'" schedule for each 28-day treatment cycle.

Reference therapy, dosage, and mode of administration: Gemcitabine (1000 mg/m^2) with cisplatin (25 mg/m^2) administered by IV infusion on Days 1 and 8 of a 21-day treatment cycle.

Duration of treatment: Treatment in each group was to be continued until radiographic evidence of progressive disease confirmed by BICR, unacceptable toxicity, or other reason for discontinuation as permitted by the protocol was observed.

Criteria for evaluation:

This abbreviated clinical study report (aCSR) represents the final formal analysis of Study QBGJ398-301. Due to early termination of the study by the sponsor, results will focus primarily on the primary and key secondary endpoints of the study which are all related to efficacy and safety.

Efficacy:

Disease progression and/or tumor response were radiographically evaluated every 8 weeks ±7 days from the first dose of study drug, regardless of drug interruption with confirmation by BICR and by the investigator using RECIST version 1.1. Responses of PR and CR were confirmed by repeat assessment performed at least 4 weeks after the criterion for response was first met. Survival status and use of new antineoplastic medications were to be followed approximately every 3 months after until the end of the study.

Safety:

The safety evaluation was based on tolerability of study treatment, AE reporting, laboratory parameters, pregnancy outcome (if applicable), ophthalmic assessments, 12-lead electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), vital signs, and ECOG performance status. Standard safety presentations were prepared, including summaries of AEs of special interest.

Statistical methods:

Efficacy:

The primary analyses for efficacy endpoints were based on the intent-to-treat (ITT) population, which included all subjects who were randomized. Subjects were analyzed by the treatment group randomized to, regardless of the treatment received.

The primary efficacy analysis endpoint was progression free survival (PFS), calculated as the number of months from randomization to radiographically confirmed disease progression as assessed by BICR, or death due to any cause, whichever was earlier. Subjects who were still alive without documented disease progression were censored at their last valid tumor assessment. For subjects who had a PFS event after missing 2 or more consecutive scheduled tumor evaluations (ie, the previous valid tumor assessment was >18 weeks prior to the event), their PFS was censored at their last valid tumor assessment. Subjects who had no qualified PFS event or any qualified post-baseline tumor assessment were censored based on their randomization date. PFS and censor calculations were limited to the initial treatment phase.

The key secondary endpoint was overall survival (OS), which was defined as the number of months from randomization to death (date of death - date of randomization + 1)/(365.25/12). Subjects who had not died (no record of death) or were lost to follow-up were censored at the date of last known to be alive. Subjects who died or were lost to follow-up during the crossover period were censored at the start date of crossover.

The other secondary efficacy variables (investigator assessed PFS and BOR, duration of response (DOR), disease control rate (DCR), and ORR by BICR and the investigator) were evaluated using appropriate methods. Briefly, BOR, defined as the best response a subject ever achieved after study treatment and prior to any subsequent anticancer therapy, was summarized separately for confirmed CR, confirmed PR, stable disease, and progressive disease (PD). Overall response rate (ORR) is defined as the proportion of subjects with BOR of either confirmed PR or confirmed CR among the ITT population with measurable disease at baseline. All subjects who did not achieve BOR of either confirmed PR or confirmed CR were considered non-responders. The DOR was defined as the time from initiation of CR or PR to PD or death. If a subject did not reach PD or death, the DOR was censored at the last valid tumor assessment. Subjects who never reached response were not included in DOR analysis.

Time to event endpoints (ie, PFS, OS, and DOR) were analyzed by Kaplan-Meier (K-M) method. With the limited number of subjects enrolled at the time of the decision to terminate the study early, the number of PFS events required to assess the efficacy objectives was not achieved to the futility of the study. No formal inferential testing of efficacy was done.

Safety:

Safety analyses were performed on the safety analysis population which included all subjects who were randomized and received at least 1 dose of study treatment. Subjects were analyzed by the treatment received.

RESULTS

This aCSR represents the final formal analysis of Study QBGJ398-301 with focus on efficacy and safety results.

Study Subjects:

A total of 48 subjects were enrolled by region: Western Europe (45.8%), North America (39.6%), and Asia (14.6%). Most subjects were white (70.8%), and most were female (60.4%). Median age of the study population was 58.5 years (range: 20 to 81 years); most subjects (70.8%) were <65 years of age. Twenty-nine subjects were treated with infigratinib, and 19 subjects received gemcitabine/cisplatin.

All study subjects had an ECOG PS classification of 0 or 1, with the majority (56.3%) having a score of "0." The majority of subjects had intrahepatic bile duct (93.8%) as the primary site of CCA with adenocarcinoma histology. The most frequently reported tumor diagnosis category was T2 for 35.4% of the subjects. The majority of subjects (72.9%) had metastasis status of M1. The median time from initial diagnosis to randomization was 2.27 months. FGFR2 local status was fusion positive (fusion partner known) for 11 (22.9%) subjects and fusion positive (Intron rearrangement) for 4 (8.3%) subjects. FGFR2 central status was fusion positive (fusion partner known) for 25 (52.1%) subjects and fusion positive (Intron rearrangement) for 0 subjects.

Proportionately, subjects in the infigratinib group were more likely to have ECOG PS scores of "0" (65.5% vs. 42.1% for gemcitabine/cisplatin), and a slightly longer median time from initial diagnosis to randomization. FGFR2 local status was fusion positive (fusion partner known) for a greater number of subjects in the infigratinib group vs. the gemcitabine/cisplatin group. FGFR2 central and local status for fusion positive (fusion partner unknown) was the same for both treatment groups.

Efficacy Results:

For the primary efficacy endpoint, an event of disease progression as assessed by BICR or death occurred in 41.4% of subjects in the infigratinib group and 36.8% in the gemcitabine/cisplatin group. The median PFS was 7.39 months for the infigratinib group and 8.02 months for the gemcitabine/ cisplatin group.

An event of disease progression, as assessed by the investigator, or death occurred in 65.5% of subjects in the infigratinib group and 42.1% in the gemcitabine/cisplatin group. The median PFS was 7.39 months for the infigratinib group and 5.19 months for the gemcitabine/cisplatin group.

For the secondary endpoint of OS, an event of death occurred in 27.6% of subjects in the infigratinib group and 15.8% of subjects in the gemcitabine/cisplatin group. The median time to OS was not evaluable for either group. The secondary endpoint of BOR as assessed by BICR, reported a confirmed partial response for 11 (37.9%) subjects in the infigratinib group and 3 (15.8%) subjects in the gemcitabine/cisplatin group. Stable disease occurred for 14 (48.3%) subjects in the infigratinib group and 11 (57.9%) subjects in the gemcitabine/cisplatin group. Two subjects in each group had progressive disease.

The overall response rate as assessed by BICR and the investigator was proportionally higher in the infigratinib group when compared to the gemcitabine/cisplatin group.

Safety Results:

Overall, the safety profile observed in this study was consistent with the expected on-target effects of and AEs described for infigratinib as well as expected AEs for subjects with advanced/metastatic or inoperable CCA.

- Among subjects treated with infigratinib, median duration of exposure to infigratinib was 6.5 months (range: 0.6, 22.7 months) compared to median duration of exposure to gemcitabine of 4.4 months (range: 1.6, 13.3 months) and 3.7 months (range: 1.6, 10.9 months) to cisplatin. Median relative dose intensity was 100% (range: 77%, 100%).
- Among subjects treated with infigratinib, nearly all subjects had a dose held or reduced (23 subjects [79.3%] each) with AEs being the primary reason leading to a prescribed dose hold/reduction for 86.2%. Study drug was permanently discontinued for 9 subjects (31.0%). Adverse events were the primary reason for dose reduction in both treatment groups.
- Overall, 100.0% of subjects in the infigratinib group had at least one treatment-emergent adverse event (TEAE). The most frequently reported TEAEs by preferred term (PT) for subjects in the infigratinib group were hyperphosphataemia (26 subjects [89.7%]; constipation (14 subjects [48.3%]); diarrhoea (13 subjects [44.8%]); and alopecia, decreased appetite, fatigue, hypophosphataemia, and palmar-plantar erythrodysaesthesia syndrome (12 subjects [41.4%] each).
  - The most frequently reported TEAEs in the gemcitabine/cisplatin group were nausea (64.7%), fatigue (47.1%), and anaemia (41.2%). For many commonly occurring TEAEs, the proportions of subjects affected within each treatment group were <20%.
- In the infigratinib group, 23 subjects (79.3%) had at least 1 AE with a maximum severity of Grade 3 or Grade 4 (combined). Grade 3 or Grade 4 AEs that occurred in ≥2 subjects were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, COVID-19, decreased appetite, and palmar-plantar erythrodysaesthesia syndrome (3 subjects [10.3%] each); and fatigue, hyperphosphatemia, stomatitis, and weight decreased (2 subjects [6.9%] each). Grade 4 treatment-emergent SAEs in the infigratinib group were hypercalcaemia and hypokalaemia (1 subject [3.4%] each). In the gemcitabine/cisplatin group, all 29 subjects (100.0%) reported TEAEs, although there were no reported treatment-emergent SAEs, serious treatment-related events, or TEAEs of special interest. Ten gemcitabine/cisplatin subjects (58.8%) had Grade 3 or 4 TEAEs including neutropenia (5 subjects [29.4%]) and anaemia (2 subjects [11.8%]).
- All 29 subjects (100.0%) had a TEAE that was assessed as related to infigratinib by the investigator and 16 subjects (94.1%) had a TEAE that was assessed as related to gemcitabine/cisplatin. In the infigratinib group, 8 subjects (27.6%) had at least one treatment-related Grade 2 AE, 20 subjects (69.0%) had at least one treatment-related Grade 3 AE, and 1 subject (3.4%) had at least one treatment-related Grade 4 AE. The most common Grade 3 or Grade 4 treatment-related AEs in the infigratinib group were ALT increased, AST increased, and palmar-plantar erythrodysaesthesia syndrome (3 subjects [10.3%] each); and stomatitis, fatigue, and hyperphosphataemia (2 subjects [6.9%]) each).
  - When TEAEs were reported by age for the infigratinib group, 21 subjects <65 years experienced TEAEs compared with 8 subjects ≥65 years. In the gemcitabine/cisplatin group, 12 subjects <65 years experienced TEAEs compared with 5 subjects ≥65 years
- Prior to crossover, subjects in the crossover group had Grade 1 or Grade 2 nonserious TEAEs. One subject had nonserious Grade 3 neutrophil count decreased. Following crossover, these events were reported as treatment related.

- Eleven subjects died during the study: 6 subjects (20.7%) in the infigratinib group died due to the study indication and 2 subjects (6.9%) died due to other causes (cause of death was unknown for one subject and one subject died due to stroke secondary to metastatic CCA). In the gemcitabine/cisplatin group, 3 subjects (17.6%) died due to the study indication. Of the 11 deaths that occurred during the study, all occurred before the crossover period. One subject in the gemcitabine/cisplatin group died during the on-treatment period due to progressive disease.
- In the infigratinib group, 10 subjects experienced SAEs. The most common SAEs were COVID-19 (6.9%) and stomatitis (6.9%). Eight subjects (27.6%) had SAEs with a maximum severity of Grade 3 and 2 subjects (6.9%) had SAEs with a maximum severity of Grade 4. The only treatment-related SAE reported in >1 subject was stomatitis (2 subjects [6.9%]). There were no treatment-emergent SAEs or treatment-related SAEs reported in the gemcitabine/cisplatin group.
- A total of 7 subjects (24.1%) in the infigratinib group had TEAEs that led to treatment discontinuation compared to 4 subjects (23.5%) in the gemcitabine/cisplatin group. In the infigratinib group, the majority of these (5 subjects [17.2%]) had an event that was Grade 3 in intensity, 1 subject (3.4%) had a Grade 4 event, and 1 subject (3.4%) had a Grade 2 event. There were no TEAEs that led to treatment discontinuation in >1 subject. Three events that led to treatment discontinuation were SAEs.
    - 21 subjects (72.4%) in the infigratinib group had at least 1 TEAE that led to dose interruption. AEs that led to dose interruption in ≥10% of all subjects were hyperphosphatemia and palmar-plantar erythrodysaesthesia syndrome.
    - 19 subjects (65.5%) had at least 1 TEAE that led to dose adjustment/reduction. AEs that led to dose reduction in ≥10% of subjects were hyperphosphataemia and hypophosphatemia. There was one SAE of eye pain that led to dose reduction.
- Most subjects in both treatment groups had a TEAE that required concomitant medication: 93.1% infigratinib and 82.4% gemcitabine/cisplatin. In the infigratinib group, half of the subjects had an event that was Grade 3 (51.7%) and 6.9% had an event that was Grade 4 in intensity. TEAEs that required concomitant medication in ≥20% of subjects were hyperphosphatemia, constipation, diarrhoea, palmar-plantar erythrodysaesthesia syndrome, dry eye, stomatitis, and arthralgia.
    - The Grade 4 events that required concomitant medication in the infigratinib group were a nonserious and SAE of hypokalaemia (1 subject [3.4%]) and an SAE of hypercalcaemia (1 subject [3.4%]).
- Hyperphosphataemia was one of the most frequently reported TEAEs (26 subjects) and treatment-related TEAEs (24 subjects). This TEAE was only reported for subjects in the infigratinib group.
- Assessment of AEs and laboratory measurements demonstrated little evidence of hepatic toxicity with infigratinib. Overall, 3 subjects (10.3%) had at least 1 occurrence of AST or ALT >3×ULN. There was a single report of alkaline phosphatase (ALP) >1.5×ULN. No subjects in either group had abnormalities in liver function tests that met the criteria for Hy's Law.
- In general, a greater percentage of subjects on infigratinib experienced a negative change in visual acuity compared to the control, and the extent of the change was greater. None of these changes were deemed clinically significant or reported as AEs.
- Changes from baseline in LVEF, QTcF, or QTcB detected for any subject were unremarkable.
- Differences observed between the 2 treatment groups in shifts of vital signs, hematology, other chemistry, and other special investigations were unremarkable.

CONCLUSIONS

At the time of the decision to terminate the study early, only 48 subjects were enrolled which rendered the study futile. Consequently, no statistical testing could be done.

Overall, the safety profile observed in this study was consistent with the expected on-target effects of and AEs described for infigratinib as well as expected AEs for subjects with advanced/metastatic or inoperable CCA. It is notable that hyperphosphataemia was one of the most frequently reported TEAEs and was only reported for subjects in the infigratinib group.

In this small sample of subjects with FGFR2–positive advanced CCA, definitive conclusions are limited; however, first-line infigratinib was well tolerated and shows efficacy consistent with that shown for previously treated patients. Because this study was terminated early, there was insufficient power for comparisons between groups; therefore, these data should be viewed with caution.

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