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.

TIMING OF ANALYSES AND REPORTING

The formal analyses completed for this study are shown in Table 1.

This abbreviated clinical study report (aCSR) represents the third and final report of study CBGJ398X2204. The interim CSR [X2204i] and the primary CSR [X2204p] were the first and second reports, respectively. The initial CSRs reported results from Cohort 1 only, the primary analysis population. This final CSR reports results from all cohorts (Cohorts 1, 2, and 3) of the study.

Initially, the final analysis of the study was to be conducted after all subjects in Cohort 2 and Cohort 3 had the potential to be assessed for at least 10 months after their initial exposure to treatment. However, following interim review of the data (as permitted by the protocol), the sponsor opted to terminate the study early due to limited efficacy in Cohort 2 and Cohort 3. Early study termination was not due to concerns about safety and had no impact on the primary efficacy analysis for the study.

Table 1: Study CBGJ398X2204 Completed Formal Analyses

Analysis	Data Set		Protocol version	Cutoff date	Status	In this CSR
	Name	Definition				
NA	NA	61 subjects treated in the study with FMI I before enrollment restricted to subjects with FGFR2 fusions (in PA2) (Cohort 1).	01	30 Jun 2016	Completed by Novartis[a] in conjunction with investigators (Javle 2018b)	No
NA	NA	After 20 subjects were treated with FMI III for at least 1 cycle: all relevant data (PK, safety, dose interruptions or reductions, efficacy) (Cohort 1).	02	Unk.	Completed by Novartis[a]	No
First formal interim analysis for Cohort 1 after PA3.	Interim Efficacy Analysis Set 1	All subjects followed ≥10 months with planned extensive PK sample collection (regardless of whether extensive PK samples actually collected) and all subjects enrolled before PA2 (Cohort 1).	06	31 May 2019	Completed by QED (data on file)	No
	FAS	All subjects who received ≥1 dose of infigratinib (Cohort 1).	06	31 May 2019	Completed by QED (data on file)	No
Second formal interim analysis for Cohort 1 after PA3.	Interim Analysis Set 2	Subjects in Cohort 1 with FGFR2 fusions who had received at least one dose of infigratinib.	06	31 Mar 2020	Completed by QED	No
	Sensitivity Analysis Set	Subjects with FGFR2 fusions who received infigratinib at the time of the first formal interim analysis and subjects who had disease progression according to BICR or ended treatment by the cutoff date for the second formal interim analysis for Cohort 1 after PA3	06	31 Mar 2020	Completed by QED	No. Results reported in Interim CSR [X2204i]

Analysis	Data Set		Protocol version	Cutoff date	Status	In this CSR
	Name	Definition				
Primary Analysis for Cohort 1.	FAS	All subjects in Cohort 1 who received at least one dose of infigratinib. Per protocol analysis was not done, according to criteria specified in the supplemental SAP ([X2204p]-Appendix 16.1.9)	06	01 Mar 2021	Completed by QED	No. Results reported in Primary CSR [X2204p]
PK	PK Analysis Set	All subjects who (a) received the planned treatment, (b) provided at least one evaluable PK concentration, and (c) did not vomit within 4 hours after the dosing of infigratinib	06	01 Mar 2021	Completed by QED	No – reported separately
Review of data for Cohort 2 and 3	FAS	A total of 15 subjects in either Cohort 2 or 3 who have been treated with FMI IV for ≥1 cycle	06	04 Aug 2021	Completed by QED	No – reported separately
Final Analysis	FAS	All subjects who received at least one dose of infigratinib (Cohorts 1, 2, and 3)	06	07 Feb 2022[b]	Completed by QED	Yes
PK	PK Analysis Set	All subjects who (a) received the planned treatment, (b) provided at least one evaluable PK concentration, and (c) did not vomit within 4 hours after the dosing of infigratinib	06	07 Feb 2022[b]	Completed by QED	No – reported separately

Abbreviations: BICR=blinded independent central review; CSR=clinical study report; FAS=Full Analysis Set; FGFR=fibroblast growth factor receptor; FMI=Final Market Image; NA=Not available; PA=protocol amendment; PK=pharmacokinetic; SAP=statistical analysis plan; Unk=Unknown.
Note: Cohort 1=subjects with FGFR2 fusions/rearrangements; Cohort 2=subjects with other FGFR alterations; Cohort 3=subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor (other than infigratinib).
[a] In January 2018, QED licensed worldwide rights to infigratinib from Novartis. Sponsorship was transferred to QED in September 2018.
[b] Last patient, last visit for the study.

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

3. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Note on terminology in this abbreviated CSR: Terminology has evolved for this program since the original protocol was written. This abbreviated CSR uses new terminology, after briefly bridging from the old terminology, so some text does not exactly reflect what appears in the protocol and statistical analysis plan (SAP). Examples include:

- The abbreviated CSR uses "rearrangement" instead of "translocation."
- "FGFR2 fusions" is used to abbreviate "FGFR2 fusions or rearrangements [formerly translocations]."
- The abbreviated CSR uses "subject" instead of "patient" when referring to subjects in this study.
- The abbreviated CSR uses "blinded independent central review (BICR)" or "BICR" instead of "central imaging review."

The exception to this is the study title, which always appears consistent with the protocol.

Abbreviation	Term/Definition
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic-pyruvic transaminase
AST/SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical
AT	umbrella term for alanine aminotransferase and aspartate aminotransferase
BGJ398	infigratinib
BICR	blinded independent central review
BMI	body mass index
BOR	best overall response
cfDNA	cell free DNA
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
CRO	contract research organization
CSR	clinical study report
CSR/RPED	central serous retinopathy/retinal pigment epithelium detachment
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FAS	Full Analysis Set

Abbreviation	Term/Definition
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FGFR1	fibroblast growth factor receptor 1
FGFR2	fibroblast growth factor receptor 2
FGFR2 fusions	FGFR2 fusions or rearrangements (formerly FGFR2 fusions or translocations); "FGFR2 fusions" is used to abbreviate this terminology
FGFR3	fibroblast growth factor receptor 3
FMI	Final Market Image
GCP	Good Clinical Practice
GI	gastrointestinal
ICH	International Council for Harmonisation
KM	Kaplan-Meier
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition
OCT	optical coherence tomography
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PS	performance status
PT	preferred term
QD	once a day
QTcB	QTc corrected by Bazett's formula
QTcF	QTc corrected by Fridericia's formula
RBC	red blood cell
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse events
ULN	upper limit of normal
WBC	white blood cell

5. ETHICS

This section is not a requirement for an abbreviated CSR per the Guidance for Industry on the Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (FDA 1999). However, for reference, this information has been previously provided in the interim CSR [X2204i-Section 5] and the primary CSR [X2204p-Section 5].

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This section is not a requirement for an abbreviated CSR per the Guidance for Industry on the Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (FDA 1999). However, for reference, this information has been previously provided in the interim CSR [X2204i-Section 6] and the primary CSR [X2204p-Section 6].

7. INTRODUCTION

Cholangiocarcinoma is a serious and life-threatening disease with very limited treatment options and an overall poor prognosis.

Infigratinib (formerly BGJ398, also known as BBP-831 and infigratinib phosphate) is an orally bioavailable, potent, selective ATP-competitive inhibitor of the fibroblast growth factors (FGFRs) 1, 2, and 3, which has demonstrated antitumor activity in nonclinical in vitro and in vivo tumor models harboring FGFR genetic alterations (data on file). Infigratinib is a tyrosine kinase inhibitor. 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).

For more detailed background information on cholangiocarcinoma and infigratinib, refer to the interim CSR [X2204i-Section 7].

The primary objective of study CBGJ398X2204 was to evaluate the efficacy of single agent infigratinib in subjects with advanced or metastatic cholangiocarcinoma with FGFR2 fusions (Cohort 1). Following a protocol amendment, additional study cohorts were added to support exploratory objectives of the study: Cohort 2 (subjects with other FGFR alterations) and Cohort 3 (subjects with FGFR2 fusions who received prior treatment with an FGFR inhibitor other than infigratinib). For the purpose of this CSR, results from subjects with other FGFR alterations enrolled to Cohort 1 under the original protocol were combined with results from subjects in Cohort 2 (subjects with other FGFR alterations) and are hereafter collectively referred to as Cohort 2.

Two CSRs have been issued for this study with focus on Cohort 1: An interim CSR [X2240i] which reported analyses conducted after all subjects in Cohort 1 had received at least 1 dose of infigratinib, and a primary CSR [X2204p] which reported results of the primary efficacy analysis of the study, conducted after all subjects in Cohort 1 had the opportunity to be followed for at least 10 months after their initial exposure to treatment. The final analysis of the study was to be conducted after all subjects in Cohort 2 and Cohort 3 had the potential to be assessed for at least 10 months after their initial exposure to treatment. However, following interim review of the data

(as permitted by the protocol), the sponsor opted to terminate the study early due to limited efficacy in Cohort 2 and Cohort 3. Early study termination was not due to concerns about safety and had no impact on the primary efficacy analysis for the study.

This final abbreviated CSR reports results from all cohorts (Cohort 1, 2, and 3) and represents the final formal analysis of Study CBGJ398X2204.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1. Objectives

8.1.1. Cohort 1

The primary objective of this study was 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.

The secondary objectives were to:

- Further evaluate the efficacy of single agent infigratinib in Cohort 1.
- Characterize the safety and tolerability of single agent infigratinib in Cohort 1.

8.1.2. Cohort 2 and Cohort 3

Two exploratory objectives apply to Cohorts 2 and 3:

- 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 (Cohort 3).
- 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 (Cohort 3).

8.1.3. Overall Study

Two secondary objectives apply for the overall study:

- Determine selected trough and 2-hour or 4-hour plasma concentrations of infigratinib and its metabolites.
- Characterize the PK profile of the infigratinib Final Market Image (FMI) III and FMI IV formulations.

One exploratory objective applies for the overall study:

- 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).

8.2. Endpoints

8.2.1. Cohort 1

The primary endpoint for this study is overall response in Cohort 1 assessed according to blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer 2009).

The secondary endpoints are:

- Overall response assessed by investigator; progression-free survival (PFS), best overall response (BOR), and disease control assessed by investigator and by BICR per RECIST version 1.1; and overall survival (OS) in Cohort 1.
- Type, frequency, and severity of adverse events (AEs) and serious adverse events (SAEs) and tolerability (dose interruptions, reductions, and intensity) in Cohort 1.

8.2.2. Cohort 2 and Cohort 3

Two exploratory endpoints apply for Cohorts 2 and 3:

- Type, frequency, and severity of AEs and SAEs and tolerability (dose interruptions, reductions, and intensity).
- PFS, overall response, BOR, response onset, and disease control assessed by the investigator per RECIST version 1.1, and OS.

8.2.3. Overall Study

Two secondary endpoints apply for the overall study:

- Selected trough and 2-hour or 4-hour plasma concentration profiles and derived PK parameters of infigratinib and its metabolites.
- For FMI III and FMI IV: Plasma concentration profiles and derived PK parameters of FMI III and FMI IV.

Two exploratory endpoints apply for the overall study:

- DNA sequencing of paired biopsies (tumor tissue) from subjects who progressed and analysis of cell free DNA (cfDNA).
- Serial serum CA19-9 levels.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design

This multicenter, open-label, 3-cohort, Phase 2 study evaluated infigratinib antitumor activity in subjects with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations. Documented evidence of FGFR gene alterations was required for enrollment. The specific

genetic alterations allowed on study were determined through molecular prescreening and subdivided into FGFR2 fusions vs other FGFR genetic alterations.

This abbreviated CSR provides methods and safety results of the final analyses of the study for Cohorts 1, 2, and 3.

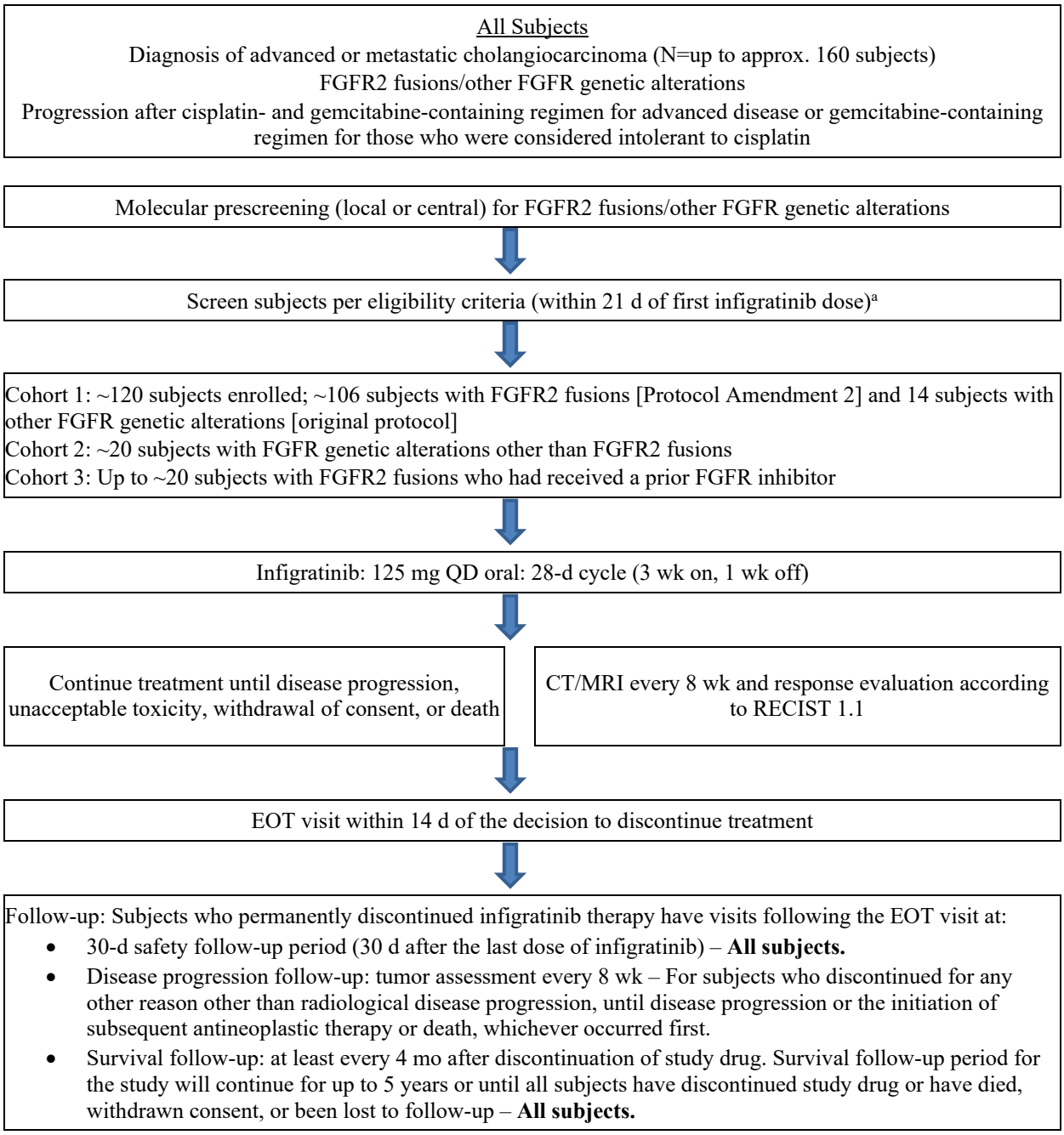
Refer to Table 1 for a summary of all analyses performed over the course of the study.

A study schematic is presented in Figure 1. The Schedule of Assessments used in the study is provide in the primary CSR [X2204p – Section 9.5].

To assess the efficacy of infigratinib, subjects were evaluated for tumor response radiographically every 8 weeks until disease progression using RECIST version 1.1 or until subjects discontinued from the study. Responses of partial response (PR) and complete response (CR) were confirmed by repeat assessment ≥4 weeks after the criterion for response was first met.

The safety evaluation was based on adverse event (AE) reporting, laboratory evaluations, vital signs, ophthalmic evaluations, electrocardiogram (ECG) and cardiac imaging assessments, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and pregnancy outcome (if applicable).

Figure 1: Study Design



Abbreviations: CT=computed tomography; d=day; EOT=end of treatment; FGFR2=fibroblast growth factor receptor 2; mo=month; MRI=magnetic resonance imaging; QD=once a day; RECIST=Response Evaluation Criteria in Solid Tumors; wk=week.

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

Source: Derived from Figure 1 in the Study Protocol [Appendix 16.1.1].

9.2. Discussion of the Study Design, including the Choice of Control Groups

9.3. Selection of Study Population

9.3.1. Inclusion Criteria

Subjects were eligible for study participation if they met each of the following inclusion criteria:

1. Histologically or cytologically confirmed cholangiocarcinoma at the time of diagnosis. Subjects with cancers of the gallbladder or ampulla of Vater were not eligible.
2. Written documentation of local or central laboratory determination of the following FGFR gene alterations from a sample collected before infigratinib treatment (according to protocol amendment 4):
   - Cohort 1: FGFR2 fusions (focus of the interim and primary CSRs)
   - Cohort 2: one of the following:
     a. FGFR1 fusions.
     b. FGFR3 fusions.
     c. FGFR1/2/3 mutation known to be an activating mutation as noted in Appendix 4 of the study protocol [Appendix 16.1.1] (for mutations not listed in Appendix 4, enrollment was allowed with written pre-approval of the QED medical monitor).
   - Cohort 3: FGFR2 fusions. (must have received prior treatment with an FGFR2 inhibitor other than infigratinib).

   (**Note**: Cohort 1 mainly consists of subjects with FGFR2 fusions; however, subjects with other FGFR genetic alterations were allowed in Cohort 1 before protocol amendment 2. To support the final analysis, those subjects enrolled to Cohort 1 with other FGFR genetic alterations were transitioned to Cohort 2 (subjects with other FGFR alterations). See the interim CSR [X2204i-Section 9.8.1] for an explanation of the different cohorts and when they were added to the study.
3. An archival tissue sample available with sufficient tumor for central FGFR gene alteration molecular testing if written documentation was provided from a local laboratory, unless agreed upon between the sponsor and the Investigator. However, if an archival tissue sample was not available, a newly obtained (before start of treatment) tumor biopsy could be submitted instead. If written documentation of FGFR gene alteration in tumor tissue was available from the central laboratory, an additional tumor sample did not need to be submitted for central FGFR gene alteration molecular testing. Note: All enrolled subjects should have had determination of FGFR gene alteration by the central laboratory as confirmation of local laboratory testing, but this central confirmation was not required before enrollment in the study.
4. Evidence of measurable disease according to RECIST version 1.1.
5. Received at least one prior regimen containing gemcitabine with or without cisplatin for advanced/metastatic disease. Subjects had to have evidence of progressive disease

following their prior regimen, or if prior treatment was discontinued due to toxicity, had to have continued evidence of measurable disease.

6. ≥18 years of age of either gender.
7. ECOG PS ≤1. Subjects with ECOG PS of 2 are considered on a case-by-case basis after discussion with the sponsor.
8. Able to read and/or understand the details of the study and provide written evidence of informed consent as approved by Institutional Review Board/Ethics Committee.
9. Recovery from AEs of previous systemic anticancer 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.
12. Cohort 3 only: documented prior treatment with FGFR inhibitor other than infigratinib.

9.3.2. Exclusion Criteria

Subjects were not eligible for study participation if they met any of the following exclusion criteria:

1. Prior or current treatment with a mitogen-activated protein kinase (MEK) inhibitor (all cohorts), 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 central nervous system tumors was allowed but had to 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 nonmelanoma carcinoma of the skin or any other curatively treated malignancy that was not expected to require treatment for recurrence during the course of the study.
4. Any other medical condition that, in the investigator's judgment, would prevent the subject'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/ulceration, or 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 infigratinib (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, and small bowel resection).
8. Current evidence of endocrine alterations of calcium/phosphate homeostasis, eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis.
9. Treatment with any of the following anticancer therapies prior to the first dose of infigratinib within the stated timeframes:
    a. Cyclical chemotherapy (intravenous [IV]) within a period of time that was shorter than the cycle length used for that treatment (eg, 6 weeks for nitrosourea, mitomycin-C).
    b. Biological therapy (eg, antibodies – including bevacizumab) within a period of time that was ≤5 $t_{1/2}$ or ≤4 weeks, whichever was shorter, prior to starting study drug.
    c. Continuous or intermittent small molecule therapeutics within a period of time that was ≤5 $t_{1/2}$ or ≤4 weeks (whichever was shorter) prior to starting study drug.
    d. Any other investigational agents within a period of time that was ≤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.
    e. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) that was ≤4 weeks or limited field radiation for palliation that was ≤2 weeks prior to starting study drug.
10. Currently receiving, or 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. Subjects were not permitted to receive enzyme-inducing anti-epileptic drugs.
11. 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.
12. Insufficient bone marrow function:
    a. Absolute neutrophil count <1,000/mm^3 (1.0×10^9/L).
    b. Platelets <75,000/mm^3 (75×10^9/L).
    c. Hemoglobin <9.0 g/dL.
13. Insufficient hepatic and renal function:
    a. Total bilirubin >1.5 × upper limit of normal (ULN) (for subjects with documented Gilbert syndrome, direct bilirubin ≤1.5 × ULN and enrollment require approval by the medical monitor).
    b. Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) >2.5 × ULN (AST and ALT >5 × ULN in the presence of liver metastases).
    c. Serum creatinine >1.5 × ULN and a calculated (using the Cockcroft-Gault formula [Cockcroft 1976]) or measured creatinine clearance of <45 mL/min.

14. Abnormal calcium or phosphorus:

    a. Inorganic phosphorus outside of normal limits.
    b. Total serum calcium (could be corrected) outside of normal limits.
    c. Calcium-phosphorus product ≥55 mg^2/dL^2.

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

    a. Congestive heart failure that required treatment (New York Heart Association ≥Grade 2), left ventricular ejection fraction (LVEF) <50% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO), or uncontrolled hypertension (refer to World Health Organization International Society of Hypertension guidelines).
    b. History or presence of clinically significant ventricular arrhythmias, atrial fibrillation, resting bradycardia, or conduction abnormality.
    c. Unstable angina pectoris or acute myocardial infarction ≤3 months prior to starting study drug.
    d. QTcF >470 msec (males and females).
    e. History of congenital long QT syndrome.

16. 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 gonadotropin laboratory test.

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

    Women of child-bearing potential and males whose sexual partners were women of child-bearing potential must have agreed to use barrier contraception and a second form of highly effective contraception (Clinical Trials Facilitation Group 2014; see Appendix 5 of the protocol [Appendix 16.1.1] while receiving study drug and for 3 months following their last dose of study drug. 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, postovulation methods) and withdrawal were not acceptable methods of contraception.

    A woman was not of child-bearing potential if she had undergone surgical sterilization (total hysterectomy, or bilateral tubal ligation or bilateral oophorectomy at least 6 weeks before taking study drug) or if she was postmenopausal and 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).

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. Males were not to father a child in this period. Use of a condom was required by vasectomized men during intercourse with a male partner in order to prevent delivery of the drug via seminal fluid.

19. Amylase or lipase >2.0 × ULN.
20. Any known hypersensitivity to calcium-lowering agents, infigratinib, or their excipients.
21. Cohort 3 only: Known existence of a V564F mutation in the FGFR2 gene.

9.4. Treatments

This section is not a requirement for an abbreviated CSR per the Guidance for Industry on the Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (FDA 1999). However, for reference, this information has been previously provided in the interim CSR [X2204i-Section 9.4] and the primary CSR [X2204p-Section 9.4].

9.5. Efficacy and Safety Variables

This section is not a requirement for an abbreviated CSR per the Guidance for Industry on the Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (FDA 1999). However, for reference, this information has been previously provided in the interim CSR [X2204i-Section 9.5] and the primary CSR [X2204p-Section 9.5].

9.6. Data Quality Assurance

This section is not a requirement for an abbreviated CSR per the Guidance for Industry on the Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (FDA 1999). However, for reference, this information has been previously provided in the interim CSR [X2204i-Section 9.6] and the primary CSR [X2204p-Section 9.6].

9.7. Statistical Methods Planned and Determination of Sample Size

This section is not a requirement for an abbreviated CSR per the Guidance for Industry on the Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (FDA 1999). However, some topics, including statistical and analytical plans, analysis populations, and safety assessments, were retained to provide context to the results presented.

9.7.1. Statistical and Analytical Plans

This section describes the analysis plan supporting the final analysis specified in SAP version 3.0, dated 13 May 2020 [X2204i-Appendix 16.1.9]. This is the same SAP supporting the interim CSR. A supplementary SAP, dated 08 April 2021, specifying additional analyses for the primary analysis of the study (for Cohort 1 only) applies only to the primary CSR [X2204p-Appendix 16.1.9].

Data were analyzed by the sponsor and/or designated contract research organization using SAS® version 9.4 in the statistical computing environment.

9.7.2. Determination of Sample Size

Refer to the Section 10.8 of the protocol [Appendix 16.1.1].

9.7.3. Analysis Populations

Refer to Table 1 for a summary of analyses performed over the course of the study. The following applies to this abbreviated CSR only.

The Full Analysis Set (FAS) was used for all analyses reported in this abbreviated CSR. The FAS included all subjects who had received ≥1 dose of infigratinib. Unless otherwise specified, the FAS was used for all listings of raw data. Subsets of the FAS analyzed for this abbreviated CSR are as follows:

- Subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS (hereafter referred to as Cohort 1) (N=108) included subjects in Cohort 1 with FGFR2 fusions or rearrangement who had received ≥1 dose of infigratinib.

  This Cohort 1 subset was the basis for analyses and results presented in the interim CSR [X2204i] and primary CSR [X2204p], unless otherwise specified.

- Subjects with other FGFR alterations in Cohort 1 FAS (enrolled under the original protocol) and Cohort 2 FAS (hereafter collectively referred to as Cohort 2) (N=25).

  This subset includes all subjects enrolled to Cohort 2 and the remaining subjects from Cohort 1 who had other FGFR gene alterations (instead of FGFR2 fusions) and who had received ≥1 dose of infigratinib. For this subset, separate analyses for safety are provided in Section 12.2 and Section 14. No efficacy analyses were done for this subset; however, 2 efficacy listings (Listing 16.2.6.2 and 16.2.6.5) were prepared.

- Subjects with FGFR2 fusions who received prior treatment with an FGFR inhibitor (other than infigratinib) in Cohort 3 FAS (hereafter referred to as Cohort 3) (N=10). For this subset, separate analyses for safety are provided in Section 12.2 and Section 14. No efficacy analyses were done for this subset; however, 2 efficacy listings (Listing 16.2.6.3 and 16.2.6.6) were prepared.

9.7.4. Efficacy Analyses

An overview of the statistical analysis plan for efficacy endpoints and detailed results of the efficacy analysis for Cohort 1 are provided in the primary CSR [X2204p-Section 9.7.1.5 and -Section 11.1, respectively].

For this report only high-level efficacy results are provided for Cohort 1 (see Section 11.1). Due to early termination of the study, only by-patient listings of efficacy endpoints and tumor responses are provided for Cohort 2 and Cohort 3 (see Appendix 16.2.6).

9.7.5. Safety Analyses

In general, summaries were provided only for the on-treatment safety assessments, which are the assessments occurring or taken during the on-treatment period.

Safety analyses were performed for subjects using the FAS for each cohort. In most cases, results from Cohort 1 remained unchanged from those reported in primary CSR [X2204p - Section 12.0]. As a result, unless otherwise specified, safety data from Cohort 1 is referenced to that document. The focus of the safety presentation for this CSR is to report results from Cohort 2 and Cohort 3.

9.7.5.1. Treatment Exposure, Tolerability, and Compliance with Study Treatment

Duration of exposure, actual cumulative dose, and relative dose intensity (RDI) were summarized. The proportions of subjects who had dose reductions or interruptions, and the reasons, were summarized as a measure of tolerability (based on the dosing page of the electronic case report form [eCRF]). A by-subject listing for exposure was prepared.

Compliance to study treatment was summarized in terms of the RDI or proportion of subjects who took a predefined percentage of the number of prescribed doses. The predefined RDI categories were ≤50%, >50 to ≤75%, >75 to ≤90%, >90 to ≤100%, and >100%. The proportion of subjects falling in each category was summarized.

9.7.5.2. Adverse Events

Adverse events (AEs) were assessed by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the MedDRA version 21.0.

AEs were considered to be treatment emergent if they occurred on or after the first administration of study treatment through date of last dose of study treatment +30 days.

Treatment-emergent adverse events (TEAEs) were summarized by system organ class (SOC) and/or preferred term (PT), severity (based on CTCAE grades). Additional summaries of TEAEs were provided based on severity, seriousness, relationship to study treatment, and action taken.

Listing of AEs and SAEs were produced, and TEAEs were flagged.

9.7.5.3. Deaths

The primary reason for death was summarized for on-treatment, posttreatment, and all deaths. Treatment-emergent AEs with a fatal outcome were summarized by SOC, PT, and grade. On-treatment deaths were also summarized by SOC and PT.

All deaths were listed, and on-treatment deaths were flagged.

9.7.5.4. Adverse Events of Special Interest

The following AEs of special interest (AESIs) were evaluated:

- Calcium phosphate homeostasis, including the subcategories of hypercalcemia, hyperphosphatemia, and hypophosphatemia.
- Eye disorder, including a subset for central serous retinopathy/retinal pigment epithelium detachment (CSR/RPED).
- Cardiac disorder.
- Acute pancreatitis.
- Pathological fracture.
- Tissue calcification.
- Vascular calcification/mineralization.

For each AESI (or its subcategory), an overall summary of the characteristics was prepared. In addition, each AESI was summarized by subcategory (as applicable), PT, and worst grade. The

search strategy for each AESI is documented in the interim CSR, SAP Section 5.2 [X2204i-Appendix 16.1.9]. For tissue calcification, calciphylaxis was added to the search strategy (see Section 9.8.2).

9.7.5.5. Minimal Critical Toxicities

Minimal critical toxicities included the following categories:

- Cardiac toxicity including QT prolongation and other ECG abnormalities.
- Hepatotoxicity.
- Nephrotoxicity.
- Hematologic toxicity.

Subject incidence of AEs indicative of potential cases of the toxicities were summarized for each of the categories.

For hepatotoxicity, in addition, abnormalities in liver function tests were summarized. Subject incidence of the following was provided:

- 3×-, 5×-, 10×-, and 20× upper limit of normal (ULN) elevations of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT).
- Any elevations of bilirubin; elevated TBL to ≥2×ULN.
- Any elevations of alkaline phosphatase (ALP) >1.5×ULN.
- Elevation of "ALT or AST" (>3×ULN) accompanied by elevated TBL (>1.5×ULN, ≥2×ULN) and ALP <2×ULN.

In addition, a listing of potential Hy's Law cases identified was provided. Potential hepatotoxicity was identified by the Hy's Law (FDA Guidance for Industry 2009) as: ALT or AST >3.0×ULN; TBL ≥2.0×ULN, ALP <2.0×ULN, and no other confounding factors, including preexisting or acute liver disease.

For cardiac toxicity, ECG findings were summarized.

9.7.5.6. Laboratory Findings

Laboratory values were graded programmatically using CTCAE version 4.03, or as otherwise specified in the SAP Section 2.7.2.2.1 [X2204i-Appendix 16.1.9].

Laboratory parameters for hematology and serum blood chemistry were summarized at baseline and each postbaseline visit. The maximum and minimum observed postbaseline values, last observed values, and changes from baseline were summarized. Shift tables for shifts in laboratory parameters from baseline to worst CTCAE grade observed postbaseline were prepared. In addition, the number and percentage of subjects with postbaseline laboratory abnormal results was presented for tests based on CTCAE grade, or normal range if CTCAE grade was not available. Incidence of potential drug-induced liver injury, based on AST, ALT, TBL, and ALP, was presented. Potential Hy's law cases were also listed.

Serum calcium was summarized in this CSR instead of corrected calcium (which was summarized in the interim CSR [X2204i-Appendix 16.1.9]).

9.7.5.7. Other Safety Findings

Ophthalmic assessments, ECG and LVEF, vital signs, and ECOG PS were summarized using descriptive statistics or categorical presentations, as appropriate.

The proportions of subjects with clinically significant changes in visual acuity (<0.1 logMAR, 0.1 to <0.2 logMAR, 0.2 to <0.3 logMAR, and ≥0.3 logMAR) and intraocular pressure (≤21 mmHg and >21 mmHg) were summarized; clinically significant abnormalities in the slit lamp, OCT, and fundoscopy examinations were also summarized.

ECG data were read and interpreted centrally. The ECG analysis was performed on all subjects who received at least one dose of infigratinib with the baseline and at least one on-treatment postbaseline ECG assessment. ECG parameters were summarized at baseline and each postbaseline visit. The maximum and minimum observed postbaseline values, last observed values, and changes from baseline were summarized.

The proportions of subjects who had notable ECG values in QT, QTcF, HR, PR, or QRS were listed and tabulated (see the interim CSR, SAP Section 2.7.3.3 for definitions of notable values [X2204i-Appendix 16.1.9]). A shift table for the overall ECG assessment from baseline to worst on-treatment value was also produced.

LVEF was summarized at baseline and each postbaseline visit. The minimum observed postbaseline values and changes from baseline were also summarized. Shift tables for minimum postbaseline LVEF were prepared. Clinically significant changes in LVEF (ie, absolute decrease from baseline >10% but <20% and LVEF ≥40% to <50%; absolute decrease from baseline ≥20% and LVEF ≥20% to <40%; LVEF <20%) were also tabulated.

The proportions of subjects with notable vital signs (high/low) were tabulated. See the interim CSR, SAP Section 2.7.3.4 for definitions of notable vital signs [X2204i-Appendix 16.1.9].

ECOG PS was summarized at baseline and each postbaseline visit. The worst observed postbaseline values, last observed values, and changes from baseline were summarized.

By-subject listings of ophthalmic assessments, LVEF, ECG, and vital signs were prepared.

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes in the Conduct of the Study

The original protocol (version 00) was dated 21 February 2014. The protocol was amended 5 times, and the most recent amended protocol is dated 15 January 2020. The important revisions are described in the interim CSR [X2204i-Section 9.8.1]. The most recent protocol and all summaries of changes are included in the appendix [Appendix 16.1.1].

Following interim review of the data from Cohort 2 and Cohort 3 (as permitted by the protocol), the sponsor opted to terminate the study early due to limited efficacy. Early study termination was not due to concerns about safety and had no impact on the primary efficacy analysis for the study (ie, Cohort 1). Results of the primary efficacy and safety analyses for Cohort 1 are reported in the primary CSR [X2204p] with high-level summary provided in this abbreviated CSR. The last patient, last visit for the study occurred on 07 February 2022.

9.8.2. Changes in the Planned Analyses

Analysis plans for this study are described and appear in the interim CSR ([X2204i-Section 9.8.2] and [X2204i-Appendix 16.1.9], respectively), along with changes in analyses regarding additional subgroups and sources for analysis of tolerability. A supplementary SAP specifying additional analyses for the primary analysis appears in the primary CSR [X2204p-Appendix 16.1.9].

Additional changes not described in the SAP [X2204i-Appendix 16.1.9] or the supplementary SAP [X2204p-Appendix 16.1.9], are further described in the primary CSR [X2204p-Section 9.8.2].

To support exploratory endpoints of the study, Cohort 2 (subjects with other FGFR alterations) and Cohort 3 (subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor other than infigratinib) were added upon implementation of protocol amendment 4. The final analysis in these cohorts was to be conducted after all subjects had the potential to be assessed for at least 10 months after their initial exposure to treatment. However, after interim review of the data (as permitted by the protocol) only limited efficacy was observed and the sponsor terminated the study early.

As a result of early termination, the focus of the final analysis of the study was changed to reporting of safety results only. For Cohort 1, there were no additional efficacy endpoints to assess, regardless of early termination. Results of the primary efficacy and safety analyses for the study (ie, Cohort 1) are reported in the primary CSR [X2204p] with high-level summaries provided in this report to add context to results reported for Cohort 2 and Cohort 3.

10. STUDY SUBJECTS

The data cutoff date for this abbreviated CSR was 07 February 2022, the date of the last subject, last visit for the study.

Changes to terminology used in this abbreviated CSR are described in Section 4.

The Full Analysis Set (FAS) includes all subjects who received at least one dose of infigratinib (N=143). The FAS is further split into the following 3 cohorts:

- Cohort 1: Subjects with FGFR2 fusions/rearrangements (N=108).

  These are the same 108 subjects as the main dataset presented in the interim CSR [X2204i] (“Interim Analysis Set 2 for Cohort 1”) and the primary CSR [X2204p] (“subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS”); the only difference between reports was the length of follow-up (an additional 11 months).

  At the time of the data cutoff for the primary CSR, all but 1 subject in Cohort 1 had completed treatment follow-up. Therefore, there are minimal differences between results reported for Cohort 1 in the primary CSR and in this report.

- Cohort 2: Subjects with other FGFR alterations other than FGFR2 gene fusions or rearrangements (N=25).

This cohort includes all 11 subjects enrolled to Cohort 2 and the 14 subjects with other FGFR alterations enrolled to Cohort 1 under the original protocol.

- Cohort 3: Subjects with FGFR2 gene fusions/rearrangements who have received a prior FGFR inhibitor other than infigratinib (N=10).

  Note that Cohorts 2 and 3 were added at protocol amendment 4 to support exploratory objectives of the study and were not included in the analyses presented in the interim CSR [X2204i] or primary CSR [X2204p].

The main focus of this CSR is to report results from Cohort 2 and Cohort 3. Cohort 1 results are also briefly discussed. However, since results from Cohort 1 remain generally unchanged from what was presented in the primary CSR, in-text summaries for this cohort are mostly provided as cross-links to the primary CSR.

Refer to Table 1 for a summary of the analyses presented and not presented in this CSR.

10.1. Subject Disposition

Subject disposition for each cohort is summarized in Table 2.

By-subject listings of disposition for each cohort are presented in Appendix 16.2.4.

As of the date of the last subject, last visit for the study (07 February 2022), all subjects had ended treatment on the study.

In Cohort 1, most subjects discontinued infigratinib treatment because of disease progression (68.5%), while 17.6% discontinued due to an AE. In Cohort 2, treatment was ended in 2 subjects due to termination of the study by the sponsor; these subjects were transitioned to a patient access program (sponsored by Helsinn [Lugano, Switzerland]) in order to continue receiving infigratinib. Otherwise, disposition for subjects in Cohort 2 and for subjects in Cohort 3 was generally similar to that observed for Cohort 1. Subjects who ended treatment due to an AE are further described in Section 12.3.1.3.1.

Table 2: Subject Disposition (Full Analysis Set)

	Cohort 1[a] (N=108) n (%)	Cohort 2[b] (N=25) n (%)	Cohort 3[c] (N=10) n (%)
Subjects received study treatment	108 (100.0)	25 (100.0)	10 (100.0)
Subjects with treatment ongoing	0	0	0
Subjects ended treatment	108 (100.0)	25 (100.0)	10 (100.0)
AE	19 (17.6)	3 (12.0)	1 (10.0)
Death	1 (0.9)[d]	2 (8.0)	0
Progressive disease	74 (68.5)[e]	16 (64.0)	8 (80.0)
Physician decision	11 (10.2)[f]	2 (8.0)	1 (10.0)
Subject decision or withdrawal of consent	3 (2.8)	0	0
Study terminated by sponsor[g]	0	2 (8.0)	0

Abbreviations: AE=adverse event; FGFR2=fibroblast growth factor receptor 2.
Note: A subject was considered to have ended treatment if "dose permanently discontinued" was flagged on the dosing form and/or on the End of Treatment form; the date of discontinuation and/or reason was filled out.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.
[d] Subject 7001026 (Cohort 1); primary cause of death was sepsis (see Section 12.3.1.1).
[e] Subject 5001006 [X2204i-Section 14.3.3] was discontinued due to progressive disease (Appendix 16.2.4.1). However, per the AE listing, treatment with study drug was discontinued due to an AE (sepsis) (Listing 14.3.2.1).
[f] Subject 5008072 [X2204i-Section 14.3.3] was discontinued due to physician's decision, over concerns of clinically progressing ascites (Appendix 16.2.4.1). Per the AE listing, treatment with study drug was discontinued due to an AE (ascites) (Listing 14.3.2.1).
[g] Subject 5001042 and Subject 5006015 were still on study when it was terminated by the sponsor (Listing 16.2.4.2) and were transitioned to a patient access program (sponsored by Helsinn [Lugano, Switzerland]) in order to continue receiving infigratinib..
Sources: Table 14.1.3.1, Table 14.1.3.2, Table 14.1.3.6.

Disposition by baseline hepatic and renal function is summarized only for Cohort 1 in the primary CSR [X2204p–Section 10.1]. This information was not provided for Cohort 2 and Cohort 3 due to the small numbers in these subgroups.

Sections 10.2 (Protocol Deviations), 10.3 (Data Sets Analyzed), and 10.4 (Demographic and Other Baseline Characteristics) are not included as these sections are not a requirement for an abbreviated CSR per the Guidance for Industry on the Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (FDA 1999). However, this information may be referenced for Cohort 1 only in the primary CSR [X2204p-Section 10].

11. EFFICACY, PHARMACOKINETIC AND BIOMARKER EVALUATION

The primary efficacy analysis for study CBGJ398X2204 was conducted when all subjects in Cohort 1 (N=108 subjects with FGFR2 fusions/rearrangements) had the potential to be assessed for at least 10 months after their initial exposure to study treatment. Results of these analyses are 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 provided in the primary CSR. Efficacy data were not re-analyzed for this abbreviated CSR.

To support exploratory endpoints of the study, Cohort 2 (subjects with other FGFR alterations) and Cohort 3 (subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor) were added upon implementation of protocol amendment 4. The final analysis in these cohorts was to be conducted after all subjects had the potential to be assessed for at least 10 months after their initial exposure to treatment. However, after interim review of the data (as permitted by the protocol) only limited efficacy was observed; the BOR in the majority of subjects was either stable disease or progressive disease. 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 in Appendix 16.2.6, however efficacy summary tables were not prepared.

11.1. Efficacy Results

11.1.1. Treatment Compliance

Treatment compliance for subjects in each cohort is summarized in Table 3.

Compliance to the study drug was summarized in terms of the RDI, defined as the ratio of actual cumulative dose to the planned cumulative dose. The predefined RDI categories were ≤50%, >50% to ≤75%, >75% to ≤90%, >90% to ≤100%, and >100%.

The mean treatment compliance among subjects in Cohort 1 was 77.6% (Table 3). Treatment compliance in Cohort 2 (80.3%) and Cohort 3 (76.7%) was generally similar to that observed in Cohort 1.

Table 3: Treatment Compliance (Relative Dose Intensity in the Full Analysis Set)

Relative dose intensity[a]	Cohort 1[b] (N=108) n (%)	Cohort 2[c] (N=25) n (%)	Cohort 3[d] (N=10) n (%)
n	108	25	10
Mean (SD), %	77.6 (17.72)	80.3 (20.82)	76.7 (22.65)
Categories, n (%)			
≤50%	5 (4.6)	3 (12.0)	1 (10.0)
>50% to ≤75%	44 (40.7)	6 (24.0)	4 (40.0)
>75% to ≤90%	24 (22.2)	7 (28.0)	2 (20.0)
>90% to ≤100%	29 (26.9)	7 (28.0)	3 (30.0)
>100%	6 (5.6)	2 (8.0)	–

Abbreviations: FAS=Full Analysis Set; FGFR2=fibroblast growth factor receptor 2; SD=standard deviation.
[a] Relative dose intensity = Actual cumulative dose (mg) / Planned cumulative dose (mg) within the actual treatment duration.
[b] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[c] Cohort 2=Subjects with other FGFR alterations.
[d] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.
Sources: Table 14.3.0.1.1, Table 14.3.0.1.2, Table 14.3.0.1.6.

11.1.2. Analysis of Efficacy Endpoints

The primary efficacy objective of the study was to evaluate overall response rate (ORR) in Cohort 1 assessed by BICR according to RECIST version 1.1. Secondary efficacy objectives were to evaluate efficacy in Cohort 1 as measured by ORR (investigator assessment), duration of response (DOR [BICR and investigator assessment]), BOR (BICR and investigator assessment), disease control rate (DCR; BICR and investigator assessment), PFS (BICR and investigator assessment), and OS. A summary of primary and secondary efficacy results assessed by BICR and the investigator, is presented in Table 4. These results are further detailed in the primary CSR [X2204p-Secton 11.1.2] and will not be repeated in this abbreviated CSR.

By-subject listings of efficacy endpoints and tumor responses for individual subjects in Cohort 2 and Cohort 3 are provided in Appendix 16.2.6 but were not further summarized.

Table 4: Summary of Primary Efficacy Results by BICR and Investigator (Subjects with FGFR2 Fusion/Rearrangement in Cohort 1)

	Assessment of Disease		Results Location
	BICR	Investigator	
Primary Endpoint, n	108		Primary CSR [X2204p]-Section 11.1.2.1
Overall response rate[a], n (%)	25 (23.1)	NA	
(95% CI)[b]	(15.6, 32.2)		
Secondary Endpoints, n		108	
Overall response rate[a], n (%)	NA	35 (32.4)	Primary CSR [X2204p]-Section 11.1.2.1
(95% CI) [b]		(23.7, 42.1)	
Duration of response[c]**, n**	25	35	Primary CSR [X2204p]-Section 11.1.2.1
Kaplan-Meier estimate			
Median, months	5.55	7.23	
95% CI	3.78, 7.66	5.16, 9.00	
Min, max, months	0.92+, 19.12	1.51+, 20.70	
≥12 months, n (%)	1 (4.0)	2 (5.7)	
≥9 to <12 months, n (%)	3 (12.0)	7 (20.0)	
≥6 to <9 months, n (%)	5 (20.0)	6 (17.1)	
<6 months	16 (64.0)	20 (57.1)	
Response onset	25	35	Primary CSR [X2204p]-Table 15
Mean (standard deviation), months	3.21 (1.71)	3.53 (3.21)	
Median, months	3.61	1.94	
Min, max: months	1.38, 7.36	1.38, 18.76	
Best overall response, n	108	108	Primary CSR [X2204p]-Section 11.1.2.2
Confirmed CR	1 (0.9)	0	
Confirmed PR	24 (22.2)	35 (32.4)	
Stable disease[d]	66 (61.1)	56 (51.9)	
Unconfirmed CR/PR	14 (13.0)	10 (9.3)	
Progressive disease	11 (10.2)	11 (10.2)	
Not Done	6 (5.6)	6 (5.6)	
Disease control rate[e]**, n**	108	108	Primary CSR [X2204p]-Section 11.1.2.3
Event, n (%)	91 (84.3)	91 (84.3)	
(95% CI)[b]	(76.0, 90.6)	(76.0, 90.6)	
Progression-free survival[d]			Primary CSR [X2204p]-Section 11.1.2.4
Event, n (%)	81 (75.0)	88 (81.5)	
Median, months	7.29	6.74	
(95% CI)	(5.59, 7.56)	(5.55, 7.56)	
Overall survival			Primary CSR [X2204p]-Section 11.1.2.5
Death event, n (%)	89 (82.4)		
Median, months (95% CI)	11.86 (10.68, 14.85)		

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CR=complete response; FGFR2=fibroblast growth factor receptor 2; NA=not applicable; PR=partial response.

+ indicates numbers reported for subjects whose response was still ongoing.

[a] Proportion with a best overall response of confirmed CR or PR.

[b] Binomial proportion with exact 95% CI.

[c] Duration of response calculated as months from initial response to disease progression or death due to any cause in confirmed responders.

[d] Progression-free survival was calculated as the number of months from the first dose of study drug to progression or death due to any cause, whichever occurred earlier. Subjects without an assessment of progression or death were censored at the last adequate tumor assessment. For subjects who had an event after ≥2 missed visits, the subject was censored at the last adequate tumor assessment before the missing visit.

Source: [X2204p – Table 15].

11.2. Results of Statistical Issues Encountered During the Analysis

See the primary CSR [X2204p-Section 11.2] for details. No additional efficacy analyses were performed to support the final abbreviated CSR.

11.3. Pharmacokinetic and Biomarker Evaluations

11.3.1. Pharmacokinetics

Results of the PK analysis are provided in a separate PK report [QEDT-NCA-BGJ398-827-v5].

11.3.2. Biomarker Analyses

Subject eligibility was confirmed by FGFR biomarker assessment. Results for Cohort 1 are summarized in the primary CSR [X2204p-Section 11.3.2]. FGFR status Cohort 2 and 3 are provided the listings of subject disposition (Listing 16.2.4.2 and 16.2.4.3, respectively).

11.4. Efficacy Summary

Overall, in the primary analysis population (Cohort 1), a clinically meaningful ORR with durable responses was observed in subjects with advanced or metastatic cholangiocarcinoma. Results for Cohort 1 are further summarized in the primary CSR [X2204p-Section 11.4].

For Cohort 2 and Cohort 3, only limited efficacy was observed; the BOR in the majority of subjects was either stable disease or progressive disease. 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 in Appendix 16.2.6, however efficacy summary tables were not prepared.

12. SAFETY EVALUATION

This section summarizes safety results for the study, as follows: exposure and tolerability (Section 12.1); most common AEs and events by severity and relationship to study drug (Section 12.2); deaths, other SAEs, and other significant AEs, including those that led to discontinuation of study drug or dose interruption or reduction and those that required concomitant medication (Section 12.3); AESIs (Section 12.4); minimal toxicities (Section 12.5); clinical laboratory investigation (Section 12.6); and vital signs, physical findings, and other observations related to safety (Section 12.7). For completeness, laboratory values relevant to the AESI of calcium phosphate homeostasis and ophthalmic assessments relevant to the AESI of ocular disorders are discussed in Section 12.4.

AEs were considered to be treatment emergent if they occurred on or after the first administration of study treatment through date of last dose of study treatment +30 days. In the body of this abbreviated CSR, treatment-emergent AEs are simply referred to as AEs, unless otherwise specified.

The main focus of this section is to report safety results from subjects in Cohort 2 (N=25) and Cohort 3 (N=10). For Cohort 1, results of the final safety analysis are generally the same as those reported in the primary CSR [X2204p-Section 12.] with only minor differences due to a single Cohort 1 subject who remained on the study after the data cutoff for the primary analysis

(01 March 2021) and as a result of minor adjustments due to data cleaning in preparation for the final analysis. These changes had no impact on the overall safety assessment but did result in minor difference from results reported previously for Cohort 1. Unless otherwise specified, only a high-level summary of results for Cohort 1 will be provided in this abbreviatd CSR with cross-link to the more detailed results reported in the primary CSR [X2204p-Section 12.].

12.1. Extent of Exposure

For information related to exposure for subjects in each cohort, see the following sources:

- Cohort 1: Table 14.3.0.1.1, Table 14.3.0.2.1, and Appendix 16.2.5.1.
- Cohort 2: Table 14.3.0.1.2, Table 14.3.0.2.2, and Appendix 16.2.5.2.
- Cohort 3: Table 14.3.0.1.6, Table 14.3.0.2.3, and Appendix 16.2.5.3.

12.1.1. Treatment Exposure

Treatment exposure for subjects in each cohort is summarized in Table 5.

For subjects in Cohort 1, median duration of exposure to infigratinib was 5.6 months (range: 0.03-40.74 months). Slightly more than half (51.9%) of the subjects were exposed to infigratinib for ≤6 months. Thirty-eight subjects (35.2%) were exposed between 6 and ≤12 months, and 14 subjects (13.0%) were exposed for >12 months. Median relative dose intensity was 77.6% (range: 38%-105%). Six subjects (5.6%) had a relative dose intensity >100%. These results remain essentially unchanged from those presented in the primary CSR except for a slightly higher maximum duration of exposure due to the 1 subject still on treatment after the cutoff date for that analysis (primary CSR maximum duration: 39.10 months; this abbreviated CSR maximum duration: 40.74 months) (X2204p-Section 12.1.1).

In Cohort 2 and Cohort 3, the median duration of exposure to infigratinib was 2.33 and 1.63 months, respectively, and most subjects received infigratinib for less than 6 months. Relative dose intensity was ~80% for each cohort.

Infigratinib exposure by baseline hepatic and renal function is provided only for Cohort 1 in the primary CSR [X2204p]. This information was not provided for Cohort 2 and Cohort 3 due to the small numbers of subjects in these subgroups.

Table 5: Summary of Infigratinib Exposure (Full Analysis Set)

	Cohort 1[a] (N=108) n (%)	Cohort 2[b] (N=25) n (%)	Cohort 3[c] (N=10) n (%)
Duration of treatment (months)			
Mean (SD)	6.82 (5.53)	5.25 (6.12)	1.98 (1.10)
Median	5.60	2.33	1.63
Min, Max	0.03, 40.74	0.46, 29.93	0.69, 4.27
≤2 months	18 (16.7)	10 (40.0)	7 (70.0)
>2 to ≤4 months	20 (18.5)	4 (16.0)	2 (20.0)
>4 to ≤6 months	18 (16.7)	2 (8.0)	1 (10.0)
>6 to ≤8 months	18 (16.7)	3 (12.0)	NA
>8 to ≤10 months	10 (9.3)	4 (16.0)	NA
>10 to ≤12 months	10 (9.3)	1 (4.0)	NA
>12 months	14 (13.0)	1 (4.0)	NA
Cumulative actual dose (mg)			
Mean (SD)	14406.0 (10246.09)	10634.0 (10525.78)	4625.0 (2611.03)
Median	12337.5	6250.0	3662.5
Min, Max	125, 65200	1750, 52350	1200, 9275
Relative dose intensity (%)[d]			
Mean (SD)	77.6 (17.72)	80.3 (20.82)	76.7 (22.65)
Median	77.6	83.3	76.4
Min, Max	38, 105	31, 105	26, 100
≤50%	5 (4.6)	3 (12.0)	1 (10.0)
>50 to ≤75%	44 (40.7)	6 (24.0)	4 (40.0)
>75 to ≤90%	24 (22.2)	7 (28.0)	2 (20.0)
> 90 to ≤100%	29 (26.9)	7 (28.0)	3 (30.0)
>100%	6 (5.6)	2 (8.0)	0

Abbreviation: FGFR2=fibroblast growth factor receptor 2; NA=not applicable; SD=standard deviation.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.
[d] Relative dose intensity=Actual cumulative dose (mg) / Planned cumulative dose (mg) within the actual treatment duration.
Source: Table 14.3.0.1.1, Table 14.3.0.1.2, Table 14.3.0.1.6.

12.1.2. Dose Interruption or Reduction

This section summarizes the proportions of subjects by cohort who had dose interruption or dose reduction of infigratinib as listed in the dose administration listings (Appendix 16.2.5). This information does not specify AEs that led to any dose interruption or dose adjustment (or reduction).

See Section 12.2.1 and Section 12.3.1.3.1 for specific information on tolerability of infigratinib based on AEs that led to discontinuation, dose interruption, or dose adjustment (or reduction) of infigratinib.

In Cohort 1, 64 subjects (59.3%) had at least 1 dose interruption and dose reduction of infigratinib; 14 (13.0%) had at least 1 dose interruption, 7 (6.5%) had at least 1 dose reduction; and 23 (21.3%) had no dose interruption or reduction (Table 14.3.0.2.1). Approximately 48.0% to 50.0% of subjects in Cohorts 2 and 3 had at least 1 dose interruption and dose reduction of infigratinib (Table 14.3.0.2.2, Table 14.3.0.2.3).

Dose Interruptions

In Cohort 1, 78 (72.2%) subjects experienced at least one dose interruption, 19 (17.6%) had 1 dose interruption, 15 (13.9%) had 2 interruptions, and 44 (40.7%) had ≥3 dose interruptions. In Cohorts 2 and 3, dose interruptions were reported in 16 (64%) and 6 (60%) subjects, respectively.

Dose Reductions

In Cohort 1, 71 (65.7%) subjects experienced a dose reduction. Doses were reduced to 75 mg/day (35 subjects [32.4%]), 100 mg/day (26 subjects [24.1%]), 50 mg/day (9 subjects [8.3%]), and 25 mg/day (1 subject [0.9%]). In Cohorts 2 and 3, dose reductions were reported in 13 (52.0%) and 6 (60.0%) subjects, respectively.

12.2. Adverse Events

Note that CTCAE Grade 5 (death) was not used in this study. Death information was collected on the death page of the eCRF.

12.2.1. Adverse Event Summary

An overview of adverse events reported across all cohorts is provided in Table 6.

In Cohort 1, 107 subjects (99.1%) had at least 1 AE, and 104 subjects (96.3%) had at least 1 treatment-related AE. Seventy-one subjects (65.7%) had at least 1 Grade 3 or Grade 4 AE (combined). Sixty-one subjects (56.5%) had at least 1 Grade 3 AE, and 10 (9.3%) had at least 1 Grade 4 AE (Table 14.3.1.2.1). Thirty-five subjects (32.4%) had a treatment-emergent SAE, of whom 9 (8.3%) had an investigator-assessed treatment-related SAE (Table 6). The treatment-related SAE that occurred in >1 subject was abdominal pain (2 subjects [1.9%]). Two subjects (1.9%) had an AE with an outcome reported as fatal; see Section 12.3.1.1 for additional details. Twenty subjects (18.5%) discontinued study drug due to an AE (per the AE eCRF). AEs that led to treatment discontinuation in ≥1 subject were subretinal fluid, fatigue, sepsis, increased aspartate aminotransferase, and increased blood creatinine (2 subjects [1.9%] each) (Table 14.3.1.2.11). Seventy-two subjects (66.7%) had dose interruption due to an AE; 65 subjects (60.2%) had a dose adjustment due to an AE (see Section 12.3.1.3 for details). Most subjects (95.4%) had an AE that required concomitant medication or non-drug therapy. These results remain generally unchanged from those presented in the primary CSR [X2204p-Section 12.2.1]. [Note: During final cleaning of the database, one event, reported in subject 5003014, was reclassified to an AE leading to dose interruption. In the initial assessment this event was classified as an AE leading to treatment discontinuation (as reported in the primary CSR). This change had no impact on the overall safety assessment but did result in minor difference from results reported previously for Cohort 1].

In Cohort 2 all 25 subjects (100%) experienced at least 1 AE, and 24 subjects (96.0%) had at least 1 treatment-related AE. Seventeen subjects (68.0%) had at least 1 Grade 3 or Grade 4 AE (combined). Fourteen subjects (56.0%) had at least 1 Grade 3 AE, and 3 (12.0%) had at least 1 Grade 4 AE (Table 14.3.1.2.2). Eleven subjects (44.0%) had a treatment-emergent SAE, of whom 2 (8%) had an investigator-assessed treatment-related SAE (Table 6). One subject (4.0%) had an AE with an outcome reported as fatal; see Section 12.3.1.1 for additional details. Three subjects (12.0%) discontinued study drug due to an AE (per the AE eCRF): visual acuity reduced, portal vein thrombosis, peripheral ischemia (Table 14.3.1.2.12). Sixteen subjects (64.0%) had dose interruption due to an AE; 9 subjects (36.0%) had a dose reduction due to an AE (see Section 12.3.1.3 for details). Most subjects (96.0%) had an AE that required concomitant medication or non-drug therapy.

In Cohort 3 all 10 subjects (100%) experienced at least 1 AE and all 10 had at least 1 treatment-related AE. Six subjects (60.0%) had at least 1 Grade 3 or Grade 4 AE (combined). Grade 3 AEs were reported in 5 of the 6 subjects (Table 14.3.1.2.21). Two subjects (20.0%) had a treatment-emergent SAE, and both had an investigator-assessed treatment-related SAE (Table 6). No subject in Cohort 3 had an AE with an outcome reported as fatal; see Section 12.3.1.1 for additional details. Two subjects (20.0%) discontinued study drug due to an AE (per the AE eCRF) (Table 14.3.1.2.26). Six subjects (60.0%) had dose interruption due to an AE; 4 subjects (40.0%) had a dose reduction due to an AE (see Section 12.3.1.3 for details). All 10 subjects (100.0%) had an AE that required concomitant medication or non-drug therapy.

AE profiles summarized by baseline hepatic and renal function are provided for Cohort 1 in the primary CSR [X2204p – Table 24]. Result for Cohort 2 and Cohort 3 were not analyzed due to the small number of subjects in these subgroups.

Table 6: Overall Summary of Adverse Events (Full Analysis Set)

	Cohort 1[a] (N=108) n (%)	**Cohort 2[b] (N=25) n (%)**	**Cohort 3[c] (N=10) n (%)**
Any AE	107 (99.1)	25 (100.0)	10 (100.0)
Grade 3 or 4 AE	71 (65.7)	17 (68.0)	6 (60.0)
AE outcome fatal	2 (1.9)	1 (4.0)	0
Serious AE (SAE)	35 (32.4)	11 (44.0)	2 (20.0)
Treatment-related AE	104 (96.3)	24 (96.0)	10 (100.0)
Serious treatment-related AE	9 (8.3)	2 (8.0)	2 (20.0)
AE leading to treatment discontinuation	20 (18.5)	3 (12.0)	2 (20.0)
AE leading to dose interruption	72 (66.7)	16 (64.0)	6 (60.0)
AE leading to dose adjustment	65 (60.2)	9 (36.0)	4 (40.0)
AE requiring concomitant medication or non-drug therapy	103 (95.4)	24 (96.0)	10 (100.0)

Abbreviations: AE=adverse event; FGFR2=fibroblast growth factor receptor 2.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.
Sources: Table 14.3.1.1.1, Table 14.3.1.1.2, Table 14.3.1.1.6.

12.2.2. Display of Adverse Events

An overview of AE tables referenced in this section is provided in Table 7.

For each cohort, AEs are summarized by overall AEs; subject incidence of AEs (overall and treatment-related, respectively) by SOC, PT, and worst grade; AEs in descending order of incidence by PT; AEs that occurred in ≥10% of subjects in descending order of incidence by PT (Cohort 1 only); incidence of Grade 3 or Grade 4 AEs (separately) by SOC, PT, and worst grade; and incidence of Grade 3 and Grade 4 AEs (combined) in descending order of incidence by preferred term.

Table 7: Adverse Events Summary Tables

Summary Table	Cohort 1[a]	Cohort 2[b]	Cohort 3[c]
Overview of AEs	Table 14.3.1.1.1	Table 14.3.1.1.2	Table 14.3.1.1.6
All AEs (SOC/PT and worst grade)	Table 14.3.1.2.1	Table 14.3.1.2.2	Table 14.3.1.2.21
All AEs (descending order of incidence by PT)	Table 14.3.1.3.1	Table 14.3.1.3.2	Table 14.3.1.3.3
Treatment-related AEs (SOC/PT and worst grade)	Table 14.3.1.2.3	Table 14.3.1.2.4	Table 14.3.1.2.22
Treatment-related AEs (descending order of incidence by PT)	Table 14.3.1.9.1	Table 14.3.1.9.2	Table 14.3.1.9.3
Common AEs (≥10% by PT) (descending order of incidence by PT)	Table 14.3.1.4.1	NA	NA
Grade 3 or 4 AEs (SOC/PT and worst grade)	Table 14.3.1.2.9	Table 14.3.1.2.10	Table 14.3.1.2.25
Grade 3 or 4 AEs (descending order of incidence by PT)	Table 14.3.1.6.1	Table 14.3.1.6.2	Table 14.3.1.6.3
Grade 3 or 4 treatment-related AEs (descending order of incidence by PT)	Table 14.3.1.11.1	Table 14.3.1.11.2	Table 14.3.1.11.3

AE=adverse event; FGFR=fibroblast growth factor receptor; NA=not available; PT=preferred term; SOC=system organ class.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.

12.2.3. Analysis of Adverse Events

12.2.3.1. Most Common Treatment-emergent Adverse Events

For subjects in Cohort 1, the highest incidences of AEs were observed in the following SOCs: Gastrointestinal Disorders (97 subjects [89.8%]), Metabolism and Nutrition Disorders (97 subjects [89.8%]), Skin and Subcutaneous Tissue Disorders (83 subjects [76.9%]), Eye Disorders (75 subjects [69.4%]), General Disorders and Administration Site Conditions (72 subjects [66.7%]), Investigations (68 subjects [63.0%]), Musculoskeletal and Connective Tissue Disorders (67 subjects [62.0%]), and Nervous System Disorders (58 subjects [53.7%]).

These results remained generally unchanged from those presented in the primary CSR (X2204p-Section 12.2.3.1).

In Cohort 2 AEs were most commonly reported for SOCs Metabolism and Nutrition Disorders (24 subjects [96.0%]), GI Disorders (20 subjects [80.0%]), General Disorders and Administration Site Conditions (16 subjects [64.0%]), Investigations (15 subjects [60.0%]), and Skin and Subcutaneous Tissue Disorders (13 subjects 52.0%]). In Cohort 3, AEs were most commonly reported for SOCs GI Disorders (9 subjects [90.0%]); Skin and Subcutaneous Tissue Disorders (8 subjects [80.0%]); Metabolism and Nutrition Disorders (7 subjects [70.0%]); Eye Disorders (6 subjects [60.0%]); and Respiratory, Thoracic and Mediastinal Disorders (6 subjects [60.0%]).

Common AEs, reported in ≥30% of subjects, are summarized in Table 8. In Cohort 1, the most commonly reported AEs were hyperphosphatemia (76.9%), stomatitis (54.6%), fatigue (40.7%), alopecia (39.8%), dry eye (36.1%), palmar-plantar erythrodysesthesia syndrome (34.3%), arthralgia (32.4%), constipation (31.5%), and dysgeusia (31.5%). Consistent with Cohort 1, hyperphosphatemia, stomatitis, and fatigue were also among the most commonly reported AEs in both Cohort 2 and Cohort 3. These AE profiles were similar across cohorts, within the margin of error for the sample size.

Table 8: Adverse Events Occurring in ≥30% of Subjects by Preferred Term (Full Analysis Set)

Preferred Term	Cohort 1[a] (N=108) n (%)	Cohort 2[b] (N=25) n (%)	Cohort 3[c] (N=10) n (%)
Hyperphosphataemia	83 (76.9)	23 (92.0)	7 (70.0)
Stomatitis	59 (54.6)	13 (52.0)	7 (70.0)
Fatigue	44 (40.7)	10 (40.0)	3 (30.0)
Alopecia	43 (39.8)	9 (36.0)	1 (10.0)
Dry eye	39 (36.1)	3 (12.0)	4 (40.0)
Palmar-plantar erythrodysaesthesia syndrome	37 (34.3)	6 (24.0)	5 (50.0)
Arthralgia	35 (32.4)	4 (16.0)	1 (10.0)
Constipation	34 (31.5)	11 (44.0)	3 (30.0)
Dysgeusia	34 (31.5)	6 (24.0)	0 (0.0)
Blood creatinine increased	27 (25.0)	8 (32.0)	1 (10.0)
Diarrhoea	27 (25.0)	8 (32.0)	3 (30.0)
Decreased appetite	26 (24.1)	7 (28.0)	3 (30.0)
Dry skin	26 (24.1)	4 (16.0)	3 (30.0)
Vomiting	25 (23.1)	5 (20.0)	3 (30.0)
Nausea	21 (19.4)	10 (40.0)	3 (30.0)
Epistaxis	19 (17.6)	5 (20.0)	6 (60.0)
Headache	19 (17.6)	4 (16.0)	3 (30.0)

Abbreviations: FGFR2=fibroblast growth factor receptor 2.
Note: Events are listed by descending order of incidence for Cohort 1; terms with the same incidence are presented in alphabetical order.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.
Sources: Table 14.3.1.4.1, Table 14.3.1.3.2, Table 14.3.1.3.3

12.2.3.2. Severity of Treatment-Emergent Adverse Events

See the primary CSR [X2204p-Section 12.2.3.2] for an overview of the severity of adverse events in Cohort 1. Results remain generally unchanged since the last report.

In Cohort 2, a total of 3 subjects (12.0%) had at least 1 AE with a maximum severity of Grade 1, 5 subjects (20.0%) had at least 1 Grade 2 AE, 14 subjects (56.0%) had at least 1 Grade 3 AE, and 3 subjects (12.0%) had at least 1 Grade 4 AE (Table 14.3.1.2.2). Seventeen subjects (68.0%) had at least 1 AE with a maximum severity of Grade 3 or Grade 4 (combined) (Table 14.3.1.6.2). Grade 3 or Grade 4 AEs that occurred in ≥2 subjects were fatigue and hypophosphatemia (3 subjects each), and anemia, arthralgia, hyperphosphatemia, hyponatremia, lipase increased, and pain in extremity (2 subjects each). Grade 4 AEs were lipase increased and sepsis in 1 subject, and intestinal ischemia and hyponatremia (1 subject each) (Table 14.3.1.2.10, Appendix 16.2.7.2). The event of lipase increased was not considered to be an SAE, but the other Grade 4 AEs were classified as serious (Table 14.3.1.2.6 and Appendix 14.3.2.2). These events are described below:

- Subject 4002027, a 59-year-old Asian male, had Grade 3 lipase increased from Day 29 through Day 42 that subsequently was changed to Grade 4 on Day 43 through Day 59. Grade 4 sepsis was also reported in this subject, with onset on Day 51 of study treatment. His last dose of study drug occurred from Day 29 to Day 47. Both events were considered not related to infigratinib. The lipase increased resolved, but the sepsis was not resolved.
- Subject 5001008, a 62-year-old white female, had Grade 4 hyponatremia with onset on Day 66. The event was not related to infigratinib. No change was made to dosing with study drug. The event was not resolved.
- Subject 5005002, a 65-year-old white female, had Grade 4 intestinal ischemia with onset on Day 345. The event was considered related to infigratinib. The outcome was fatal.

In Cohort 3, 4 subjects (40.0%) had at least 1 AE with maximum severity of Grade 2, 5 subjects (50.0%) had at least 1 Grade 3 AE, and 1 subject (10.0%) had at least 1 Grade 4 AE (Table 14.3.1.2.21). Of the 6 subjects (60.0%) who had at least 1 AE with a maximum severity of Grade 3 or Grade 4 (combined) (Table 14.3.1.6.3), the AEs that occurred in ≥2 subjects were hyperphosphatemia, hypophosphatemia, and palmar-plantar erythrodysesthesia syndrome (2 subjects each). The single Grade 4 AE was cataract (Table 14.3.1.2.25, Appendix 16.2.7.3). There were no Grade 4 AEs classified as serious (Table 14.3.1.2.23).

12.2.3.3. Treatment-related Treatment-emergent Adverse Events

See the primary CSR [X2204p-Section 12.2.3.3] for a summary of the severity of treatment-related adverse events in Cohort 1. Results remain unchanged since the last report.

In Cohort 2, a total of 24 subjects (96.0%) had an AE that was assessed as related to infigratinib by the investigator. The most common treatment-related AEs were hyperphosphatemia (22 subjects [88.0%]); stomatitis (11 subjects [44.0%]); fatigue (8 subjects [32.0%]); alopecia and nausea (7 subjects each [28.0%]); and dry mouth, dysgeusia, and palmar-plantar erythrodysesthesia syndrome (6 subjects each [24.0%]) (Table 14.3.1.9.2). Most of these AEs

(eg, hyperphosphatemia, stomatitis, palmar-plantar erythrodysesthesia syndrome) assessed as related to infigratinib are considered on-target effects of FGFR1-3 inhibition. Overall, 5 subjects (20.0%) had at least 1 treatment-related AE with a maximum severity of Grade 1, 8 subjects (32.0%) had at least 1 treatment-related Grade 2 AE, 10 subjects (40.0%) had at least 1 treatment-related Grade 3 AE, and 1 subject (4.0%) had at least 1 treatment-related Grade 4 AE (Table 14.3.1.2.4). Eleven subjects (44.0%) had at least 1 treatment-related AE with a maximum severity of Grade 3 or Grade 4 (combined) (Table 14.3.1.11.2). The most common Grade 3 or Grade 4 treatment-related AEs were arthralgia and hyperphosphatemia (2 subjects each [8.0%]) (Table 14.3.1.11.2). All other Grade 3 or Grade 4 AEs were reported in 1 subject each. The single Grade 4 treatment-related SAE, intestinal ischemia, resulted in a fatal outcome (Table 14.3.1.2.8, Listing 14.3.2.2). See Section 12.3.1.1 for further details on fatal AEs.

In Cohort 3, all 10 subjects had an AE that was assessed as related to infigratinib by the investigator. The most common treatment-related AE was stomatitis (7 subjects), followed by hyperphosphatemia (6 subjects), and epistaxis and palmer-plantar erythrodysesthesia syndrome (5 subjects each) (Table 14.3.1.9.3). Overall, 1 subject had at least 1 treatment-related AE with a maximum severity of Grade 1, 3 subjects had at least 1 treatment-related Grade 2 AE, and 6 subjects had at least 1 treatment-related Grade 3 AE. None of the treatment-related AEs were classified as Grade 4 in severity (Table 14.3.1.2.22). Of the Grade 3 AEs, hyperphosphatemia and palmar-plantar erythrodysesthesia syndrome were reported in 2 subjects each. Fatigue, gastroesophageal reflux disease, headache, hypophosphatemia, nausea, or vomiting were reported in 1 subject each (Table 14.3.1.11.3). Four of the Grade 3 AEs (gastroesophageal reflux disease, nausea, vomiting [Subject 5010004-Listing 16.2.7.3] and hypophosphatemia [Subject 4501016]) were serious (Table 14.3.1.2.24). See Section 12.3.1.2.2 for further details on treatment-related SAEs.

12.2.4. Adverse Event Listing

By-subject listings of all AEs by cohort are provided in Appendix 16.2.7.

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

An overview of tables and listings referenced in this section is provided in Table 9.

For each cohort, SAEs are summarized by subject incidence in descending order by PT and by SOC, PT, and worst grade (for both overall SAEs and treatment-related SAEs, respectively). AEs leading to discontinuation and AEs requiring concomitant therapy are also summarized by subject incidence in descending order by PT and by SOC, PT, and worst grade. AEs leading to dose interruption and AEs leading to dose adjustment are summarized by SOC, PT, and worst grade. On-treatment deaths and AEs with fatal outcomes are summarize by SOC and PT. An overview of the primary reason for death is also provided.

Unless otherwise specified, in-text summaries for Cohort 1 are cross-referenced to the primary CSR [X2204p – Section 12.3] since data are generally unchanged.

Table 9: Tables and Listings for Deaths, SAEs, and Other Significant AEs

Table/Listing	Cohort 1[a]	Cohort 2[b]	Cohort 3[c]
All SAEs			
SOC/PT and worst grade	Table 14.3.1.2.5	Table 14.3.1.2.6	Table 14.3.1.2.23
Descending order of incidence by PT	Table 14.3.1.5.1	Table 14.3.1.5.2	Table 14.3.1.5.3
Listing	Listing 14.3.2.1	Listing 14.3.2.2	Listing 14.3.2.3
Treatment-related SAEs			
SOC/PT and worst grade	Table 14.3.1.2.7	Table 14.3.1.2.8	Table 14.3.1.2.24
Descending order of incidence by PT	Table 14.3.1.10.1	Table 14.3.1.10.2	Table 14.3.1.10.3
AEs leading to treatment discontinuation			
SOC/PT and worst grade	Table 14.3.1.2.11	Table 14.3.1.2.12	Table 14.3.1.2.26
Descending order of incidence by PT	Table 14.3.1.7.1	Table 14.3.1.7.2	Table 14.3.1.7.3
Listing	Appendix 16.2.7.3	Appendix 16.2.7.4	Appendix 16.2.7.5
AEs requiring concomitant therapy or non-drug therapy			
SOC/PT and worst grade	Table 14.3.1.2.13	Table 14.3.1.2.14	Table 14.3.1.2.27
Descending order of incidence by PT	Table 14.3.1.8.1	Table 14.3.1.8.2	Table 14.3.1.8.3
Deaths			
AEs with fatal outcome (SOC and PT)	Table 14.3.1.2.15	Table 14.3.1.2.16	Table 14.3.1.2.28
On-treatment deaths (SOC and PT)	Table 14.3.1.13.3	Table 14.3.1.13.4	Table 14.3.1.13.6
Primary reason for death	Table 14.3.1.13.1	Table 14.3.1.13.2	Table 14.3.1.13.5
Death due to reason other than indication	Listing 14.3.2.7	Listing 14.3.2.8	Listing 14.3.2.9
Listing (All deaths)	Listing 14.3.2.4	Listing 14.3.2.5	Listing 14.3.2.6
AEs leading to dose interruption			
SOC/PT and worst grade	Table 14.3.1.2.17	Table 14.3.1.2.18	Table 14.3.1.2.29
AEs leading to dose adjustment			
SOC/PT and worst grade	Table 14.3.1.2.19	Table 14.3.1.2.20	Table 14.3.1.2.30

Abbreviations: AE=adverse event; FGFR=fibroblast growth factor receptor; PT=preferred term; SAE=serious adverse event; SOC=system organ class.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.

12.3.1. Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1. Deaths

Table 10 summarizes the primary reasons for deaths that occurred during the study. The on-treatment period was defined as the period of time from the day of first dose to the day of last dose +30 days (inclusive). The posttreatment period was defined as any time after the day of last dose +30 days.

In Cohort 1, 93 subjects (86.1%) died during the study: 83 subjects (76.9%) died due to the study indication (cholangiocarcinoma) and 10 subjects (9.3%) died due to other causes. Of the

93 deaths that occurred during the study, 87 (80.6%) occurred during the posttreatment period, and 6 (5.6%) occurred during the on-treatment period. The 6 deaths that occurred during the on-treatment period were due to the study indication. See the primary CSR [X2204p – Section 12.3.1.1] for further details on these on-treatment dates deaths reported in Cohort 1. Of note, a seventh subject (Subject 7001026) had an on-treatment AE with a fatal outcome (Grade 4 sepsis, not related to study treatment). The subject died 35 days after her last study treatment, so her death was not captured as on-treatment; the AE of sepsis that led to death started 7 days after the last study treatment (Table 14.3.1.2.15). A brief summary for this subject is presented in the primary CSR [X2204p – Section 12.3.1.1].

In Cohort 2, 19 subjects (76.0%) died during the study: 16 subjects (64.0%) died due to the study indication and 3 subjects (12.0%) died due to other causes (described below). Of the 19 deaths that occurred during the study, 16 (64.0%) occurred during the posttreatment period, and 3 (12.0%) occurred during the on-treatment period. Two of the 3 deaths that occurred during the on-treatment period were due to the study indication. The third was due to other causes (intestinal ischemia).

- Subject 5001031, a 60-year-old white male, had acute respiratory failure with onset on Day 495. His treatment end day was Day 216.
- Subject 5003015, a 50-year-old white female, died (cause of death unknown) on Day 1286. Her treatment end day was Day 218.
- Subject 5005002, a 65-year-old white female, had Grade 4 intestinal ischemia with onset on Day 345. Her treatment end day was Day 329. The event was considered related to infigratinib. The outcome was fatal.

In Cohort 3, 7 of the 10 subjects died during the study (Listing 14.3.2.6). All deaths occurred during the posttreatment period, and all were due to the study indication.

For further details about subject deaths by cohort, see Section 14.3.1.13 and Section 14.3.2.

Table 10: Primary Reasons for Death (Full Analysis Set)

Category	Cohort 1[a] (N=108) n (%)	Cohort 2[b] (N=25) n (%)	Cohort 3[c] (N=10) n (%)
Overall Death	93 (86.1)	19 (76.0)	7 (70.0)
Study Indication	83 (76.9)	16 (64.0)	7 (70.0)
Other	10 (9.3)	3 (12.0)	0
Death during the on-treatment period	6[d] (5.6)	3 (12.0)	0
Study Indication	6 (5.6)	2 (8.0)	0
Other	0	1 (4.0)	0
Death during the posttreatment period	87 (80.6)	16 (64.0)	7 (70.0)
Study Indication	77 (71.3)	14 (56.0)	7 (70.0)
Other	10 (9.3)	2 (8.0)	0

Abbreviations: AE=adverse events; FGFR2=fibroblast growth factor receptor 2.
Note: The on-treatment period is defined as from first dose day to last dose day +30 (inclusive); the posttreatment period is defined as any time after last dose day + 30 days.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.
[d] A seventh subject (Subject 7001026) had an on-treatment AE with a fatal outcome (Grade 4 sepsis). The subject died 35 days after her last study treatment, so the death was not summarized here as on-treatment, but the AE of sepsis that led to death started 7 days after the last study treatment. In this table, this subject is included in the category "Other" under "Death during the posttreatment period."
Source: Table 14.3.1.13.1, Table 14.3.1.13.2, Table 14.3.1.13.5

12.3.1.2. Other Serious Adverse Events

12.3.1.2.1. Most Common Serious Adverse Events

See the primary CSR [X2204p-Section 12.3.1.2.1] for a summary of SAEs in Cohort 1. Results remain unchanged since the last report [X2204p-Table 14.3.1.2.5].

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. Overall, 2 subjects (8.0%) had a Grade 1 SAE, 1 subject (4.0%) had at least 1 SAE with a maximum severity of Grade 2, 5 subjects (20.0%) had at least 1 Grade 3 SAE, and 3 subjects (12.0%) had at least 1 Grade 4 SAE (Table 14.3.1.2.6). None of the Grade 3 or 4 AEs occurred in more than 1 subject. Grade 4 SAEs consisted of sepsis (Subject 4002027) and hyponatremia (Subject 5001008), both events were considered not recovered and not resolved; and intestinal ischemia (Subject 5005002), which resulted in death (See Section 12.3.1.1 for further details).

In Cohort 3, 5 SAEs were reported for 2 subjects (20.0%): ascites, gastroesophageal reflux disease, hypophosphatemia, nausea, and vomiting. All SAEs were considered Grade 3 (Table 14.3.1.2.23) and all events had either recovered or the event resolved.

For further details about SAEs by cohort, see Section 14.3.1.5 and Section 14.3.2.

12.3.1.2.2. Treatment-Related Serious Adverse Events

See the primary CSR [X2204p-Section 12.3.1.2.2] for a summary of SAEs in Cohort 1. Results remain unchanged since the last report.

In Cohort 2, a total of 4 treatment-related SAEs were reported in 2 subjects: intestinal ischemia, arthralgia, muscular weakness, and peripheral ischemia (Table 14.3.1.10.2). With the exception of Grade 4 intestinal ischemia (further described in Section 12.3.1.1 and Section 12.2.3.2), all treatment-related SAEs were classified as Grade 2 or Grade 3 in severity and all had recovered or resolved.

- Subject 5005002, a 65-year-old white female, had treatment-related SAE of Grade 4 intestinal ischemia with onset on Study Day 345, and the subject died the same day. The subject had completed her last dose of study drug on Day 329.
- Subject 5001031, a 60-year-old white male, had treatment-related SAEs of:
  - Grade 3 arthralgia with onset on Study Day 70 and resolution on Day 83, for which treatment was reduced and the event resolved, and Grade 2 arthralgia with onset on Day 188 for which the dose was reduced and the event resolved on Day 193.
  - Grade 2 muscular weakness with onset on Study Day 70 with resolution on Day 83 for which treatment was interrupted, then reemerging on Study Day 188 with resolution on Day 193 with no dose change.
  - Grade 3 peripheral ischemia with onset on Study Day 221 (the last dose before SAE and the subject's last dose of study drug was Study Day 216), for which treatment was withdrawn and the event resolved on Day 288.

In Cohort 3, a total of 4 treatment-related SAEs were reported in 2 subjects: gastroesophageal reflux disease, nausea, vomiting (all reported in Subject 5010004), and hypophosphatemia. Both subjects who had treatment-related Grade 3 SAEs recovered or the event resolved.

- Subject 4501016, a 61-year-old white female, had a treatment-related SAE of Grade 3 hypophosphatemia with onset on Study Day 29. Treatment with study drug was interrupted, and the event resolved on Study Day 36.
- Subject 5010004, a 54-year-old white female, had treatment-related SAEs of Grade 3 gastroesophageal reflux disease, nausea, and vomiting, all with onset on Study Day 17. Treatment with study drug was reduced for these events and they all resolved on Study Day 18.

For further details about treatment-related SAEs by cohort, see Section 14.3.1 and Section 14.3.2.

12.3.1.3. Other Significant Adverse Events

12.3.1.3.1. Adverse Events that Led to Treatment Discontinuation

See the primary CSR [X2204p-Section 12.3.1.3.1] for a summary of AEs leading to treatment discontinuation in Cohort 1. Results remain generally unchanged since the last report with the

exception of 1 subject in Cohort 1 (Subject 5003014), reported in the primary CSR to have a Grade 2 AE of constipation. During final cleaning of the database, this event was determined not to have resulted in treatment discontinuation but only treatment interruption. Therefore, for Cohort 1, AEs leading to treatment discontinuation were reported for a total of 20 subjects (not 21 subjects as reported in the primary CSR) (Table 14.3.1.2.11).

In Cohort 2, 3 subjects (12.0%) each had 1 AE that led to treatment discontinuation: visual acuity reduced, portal vein thrombosis, and peripheral ischemia (Table 14.3.1.2.12). All were classified as Grade 3 in severity.

In Cohort 3, 2 subjects had a total of 10 AEs that led to treatment discontinuation. Subject 4501016 had ascites, stomatitis, pyrexia, enterocolitis infectious, vulvovaginal candidiasis, hypercalcemia, hyperphosphatemia, flank pain, palmar-plantar erythrodysesthesia syndrome (2 reports), and Subject 8001040 had treatment discontinued due to visual acuity reduced (Table 14.3.1.2.26, Listing 16.2.7.3). Three of the AEs were classified as Grade 1 in severity, 3 were Grade 2, and 4 were Grade 3.

For further details about AEs that led to treatment discontinuation for subjects in Cohort 2 and Cohort 3, see Section 14.3.1.2 and Appendix 16.2.7.

Case narratives for subjects with AEs that led to treatment discontinuation are presented in Section 14.3.3.

12.3.1.3.2. Adverse Events that Led to Dose Interruption or Adjustment

See the primary CSR [X2204p-Section 12.3.1.3.2] for a summary of AEs leading to dose interruption or adjustment in Cohort 1. Results remain generally unchanged since the last report with exception of results from Subject 5003014 as described in Section 12.3.1.3.1 (Table 14.3.1.2.17 and Table 14.3.1.2.19). Dose interruption or adjustment due to an AE was reported in 66.7% and 60.2% of subjects in Cohort 1, respectively. The most common AE that led to dose interruption or dose adjustment was hyperphosphatemia (25.0%, interruption; 25.9%, adjustment).

Dose Interruption

In Cohort 2, 16 subjects (64.0%) had at least 1 AE that led to dose interruption (Table 14.3.1.2.18). Of these, 9 subjects (36.0%) had at least 1 Grade 3 event, and there were no Grade 4 events. Hyperphosphatemia was the most commonly reported AE leading to dose interruption (5 subjects [20.0%]). No other AEs were reported in more than 1 subject.

In Cohort 3, 6 subjects (60%) had at least 1 AE that led to dose interruption (Table 14.3.1.2.29). Of these, 3 subjects (30.0%) had at least 1 Grade 3 event, and 1 subject (10.0%) had a Grade 4 event. Hyperphosphatemia, hypophosphatemia, and palmar-plantar erythrodysesthesia syndrome (2 subjects each) were the only AEs reported in more than 1 subject. Three subjects experienced a total of 8 Grade 3 events (ascites, fatigue, hyperphosphatemia, hypophosphatemia [2 events], palmar-plantar erythrodysesthesia syndrome [3 events]). One Grade 4 event (cataract) was reported in 1 subject.

Dose Adjustment

For Cohort 2, 9 subjects (36.0%) had at least 1 AE that led to dose adjustment (Table 14.3.1.2.20); 5 (20.0%) had at least 1 Grade 3 event and none had a Grade 4 event. Hyperphosphatemia (3 subjects [12.0%]) and arthralgia (2 subjects [8.0%] were the most commonly reported AEs that led to dose adjustment. No other AEs were reported in more than 1 subject.

In Cohort 3, 4 subjects (40.0%) had at least 1 AE that led to dose adjustment (Table 14.3.1.2.30); 3 subjects (30.0%) had at least 1 Grade 3 event and none had a Grade 4 event. PTs of gastroesophageal reflux disease, nausea, vomiting, blood creatinine increased, hyperphosphatemia, and palmar-plantar erythrodysesthesia syndrome were reported; none in more than 1 subject.

For further details about AEs that led to dose interruption or reduction by cohort, see Section 14.3.1.2.

12.3.1.3.3. Adverse Events that Required Concomitant Medication or Non-drug Therapy

See the primary CSR [X2204p-Section 12.3.1.3.3] for a summary of AEs that required concomitant medication for non-drug therapy in Cohort 1. Results remain unchanged since the last report (Table 14.3.1.2.13).

In Cohort 2, most subjects (96.0%) had an AE that required concomitant medication or non-drug therapy; 9 subjects (36.0%) had an event that was Grade 3 in intensity and 2 subjects (8.0%) had an event that was Grade 4 in intensity (Table 14.3.1.2.14). Hyperphosphatemia (18 subjects [72.0%]) was the most commonly reported AE requiring concomitant medication or non-drug therapy. Other AEs, reported in more than 2 subjects were: constipation, nausea, and stomatitis (7 subjects each [28.0%]), and anemia and diarrhea (3 subjects each [12.0%]). The Grade 4 AEs that required concomitant medication or non-drug therapy, intestinal ischemia and sepsis, also led to a fatal outcome. See Section 12.2.3.2 and Section 12.3.1.1 for further details.

In Cohort 3, all 10 subjects had an AE that required concomitant medication or non-drug therapy (Table 14.3.1.2.27). The most commonly reported AEs (>2 subjects) requiring concomitant medication or non-drug therapy were: hyperphosphatemia (6 subjects), and diarrhea, stomatitis, and palmar-plantar erythrodysesthesia syndrome (3 subjects each). Five subjects had at least 1 Grade 3 event and 1 subject had a Grade 4 event (cataract).

For further details about AEs that required concomitant medication or non-drug therapy by cohort, see Section 14.3.1.2.

12.3.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Section 14.3.3 presents narratives for deaths, SAEs, discontinuations of study treatment due to an AE, and selected AESIs reported between the clinical cutoff for the primary CSR (01 March 2021) to the end of the study (last patient, last visit 07 February 2022).

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

A total of 119 subjects (83.2%) died during the study, primarily due to study indication (74.1%). Most subjects (76.9%) died during the posttreatment period. For Cohort 1, 93 subjects (86.1%) died: 83 (76.9%) died due to the study indication and 10 (9.3%) died due to other causes. Six of the deaths occurred during the on-treatment period (all due to study indication). For Cohort 2, 19 subjects (76.0%) died: 3 (12.0%) died during the on-treatment period and 16 (64.0%) during posttreatment; most died due to study indication (64.0%). For Cohort 3, 7 subjects (70.0%) died, all due to study indication and all occurring during the posttreatment period.

Treatment-emergent SAEs were reported in 35 subject (32.4%) in Cohort 1 and 9 subjects (8.3%) had at least 1 treatment-related SAE. Treatment-emergent SAEs were reported in 11 subjects in Cohort 2 (with treatment-related SAEs reported in 2 subjects), and in 2 subjects in Cohort 3 (both subjects had SAEs all of which were considered treatment-related).

Overall, the most common SAEs observed were consistent with the on-target effects of FGFR1-3 inhibition and/or underlying study indication.

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%). The treatment-related SAE that occurred in >1 subject was abdominal pain (2 subjects [1.9%]). SAEs reported for Cohort 2 and Cohort 3 were generally consistent with those observed for Cohort 1. However, most PTs were reported in only 1 subject, with the exception of pyrexia (2 subjects in Cohort 2).

A total of 20 subjects (18.5%) in Cohort 1 discontinued study drug due to an AE; events that led to treatment discontinuation in >1 subject were subretinal fluid, fatigue, sepsis, increased aspartate aminotransferase, and increased blood creatinine (1.9% each). Results for Cohort 2 and Cohort 3 were generally similar, with 12.0% to 20.0% of subjects, respectively, discontinuing study treatment due to an AE.

12.4. Adverse Events of Special Interest

AESIs were prespecified in the interim SAP, version 3 [X2204i – Appendix 16.1.9]. A high-level summary of AESIs across all cohorts is provided in Table 11.

The incidences of prespecified AESIs in Cohort 1 were generally unchanged from those reported in the primary CSR [X2204p – Section 12.4] with the exceptions of 1 new report each of acute pancreatitis and pathological fracture.

AESIs reported for Cohort 2 and Cohort 3 were generally similar to those reported for Cohort 1. Given the small sample sizes in Cohort 2 and Cohort 3 in particular, the incidence of AESIs were not further characterized.

For additional information related to all AESIs, see Section 14.3.1.14, and in Section 14.3.1.16 through Section 14.3.1.24).

Table 11: Adverse Events of Special Interest (Full Analysis Set)

Category/ Sub-category	Cohort 1[a] (N=108) n (%)	Cohort 2[b] (N=25) n (%)	Cohort 3[c] (N=10) n (%)
Calcium Phosphate Homeostasis[d]	92 (85.2)	23 (92.0)	7 (70.00)
Hypercalcaemia	29 (26.9)	5 (20.0)	1 (10.0)
Hyperphosphataemia	84 (77.8)	23 (92.0)	7 (70.0)
Hypophosphataemia	25 (23.1)	5 (20.0)	2 (20.0)
Cardiac Disorder (Broad)[e]	24 (22.2)	5 (20.0)	1 (10.0)
Arrhythmia related investigations, signs, and symptoms	5 (4.6)	1 (4.0)	0
Cardiac failure	20 (18.5)	4 (16.0)	1 (10.0)
Eye Disorder, except CSR/RPED	74 (68.5)	11 (44.0)	6 (60.0)
CSR/RPED	18 (16.7)	2 (8.0)	1 (10.0)
Tissue Calcification	4 (3.7)	0	0
Pathological Fracture	2 (1.9)	1 (4.0)	0
Acute Pancreatitis (Narrow)[f]	2 (1.9)	0	0
Vascular Calcification/Mineralization	1 (0.9)	0	0

Abbreviations: CSR/RPED=central serous retinopathy/ retinal pigment epithelial dystrophy; FGFR2=fibroblast growth factor receptor 2.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.
[d] Subjects may have had >1 type of event related to calcium phosphate homeostasis.
[e] Subjects may have had >1 type of event related to cardiac disorder.
Source: Table 14.3.1.14.1, Table 14.3.1.14.2, Table 14.3.1.14.3.

12.4.1. Calcium Phosphate Homeostasis

See the primary CSR [X2204p-Section 12.4.1] for a summary of results for calcium phosphate homeostasis in Cohort 1. Results remain unchanged since the last report.

Primary CSR Section 12.4.1 includes detailed summaries of hyperphosphatemia [X2204p-Section 12.4.1.1.1], hypophosphatemia [X2204p-Section 12.4.1.1.2], hypercalcemia [X2204p-Section 12.4.1.1.3], and analyses of supporting laboratory results, including changes from baseline, abnormalities, and shifts for these analytes [X2204p-Section 12.4.1.2].

Tables further characterizing these AESIs for Cohort 1 are also provided in Tables 14.3.1.16.1, 14.3.1.33.1, 14.3.1.33.2, and 14.3.1.33.3.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

12.4.2. Ocular Disorders

See the primary CSR [X2204p-Section 12.4.2] for a summary of results for ocular disorders in Cohort 1. Results remain unchanged since the last report.

Primary CSR Section 12.4.2 includes detailed summaries of eye disorders, including CSR/RPED [X2204p-Section 12.4.2.1], CSR/RPED [X2204p-Section 12.4.2.2], and supporting ophthalmic results including clinically significant slit-lamp and fundus findings [X2204p-Section 12.4.2.3].

Tables further characterizing these AESIs for Cohort 1 are also provided in Tables 14.3.1.17.1, 14.3.1.33.4, and 14.1.33.11.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

12.4.3. Cardiac Disorder (Broad)

See the primary CSR [X2204p-Section 12.4.3] for a summary of results for cardiac disorders (broad) in Cohort 1. Results remain unchanged since the last report.

Tables further characterizing these AESIs for Cohort 1 are also provided in Tables 14.3.1.19.1 and 14.3.1.33.6.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

12.4.4. Acute Pancreatitis (Narrow)

See the primary CSR [X2204p-Section 12.4.4] for a summary of results for acute pancreatitis (narrow) in Cohort 1. Results remain generally unchanged since the last report with the exception of 1 new report of acute pancreatitis (Narrow) for a subject in Cohort 1, bringing the total to 2 subjects (1.9%).

Tables further characterizing these AESIs for Cohort 1 are also provided in Tables 14.3.1.20.1 and 14.3.1.33.7.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

12.4.5. Pathological Fracture

See the primary CSR [X2204p-Section 12.4.5] for a summary of results for pathological fracture in Cohort 1. Results remain generally unchanged since the last report, with the exception of 1 new report of pathological fracture for a subject in Cohort 1, bringing the total to 2 subjects (1.9%).

Tables further characterizing these AESIs for Cohort 1 are also provided in Tables 14.3.1.21.1 and 14.3.1.33.9.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

12.4.6. Tissue Calcification

See the primary CSR [X2204p-Section 12.4.6] for a summary of results for tissue calcification in Cohort 1. Results remain unchanged since the last report.

Tables further characterizing these AESIs for Cohort 1 are also provided in Tables 14.3.1.22.1 and 14.3.1.33.10.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

12.4.7. Vascular Calcification/Mineralization

See the primary CSR [X2204p-Section 12.4.7] for a summary of results for vascular calcification/mineralization in Cohort 1. Results remain unchanged since the last report.

Tables further characterizing these AESIs for Cohort 1 are also provided in Tables 14.3.1.24.1 and 14.3.1.33.12.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

12.5. Minimal Toxicities

A high-level summary of prespecified minimal toxicities of special interest across cohorts is provided in Table 12.

The incidences of minimal toxicities in Cohort 1 were unchanged from those reported in the primary CSR [X2204p – Section 12.5].

Minimal toxicities reported for Cohort 2 and Cohort 3 were generally similar to those reported for Cohort 1. Given the small sample sizes in Cohort 2 and Cohort 3 in particular, the incidence of minimal toxicities was not further characterized for these cohorts.

Table 12: Treatment-Emergent Potential Minimal Toxicities of Special Interest (Full Analysis Set)

Category/ Sub-category	Cohort 1[a] (N=108) n (%)	Cohort 2[b] (N=25) n (%)	Cohort 3[c] (N=10) n (%)
Cardiac Toxicity (Broad)	0	1 (4.0)	0
Haematologic Toxicity (Broad)	27 (25.0)	9 (36.0)	0
Haematopoietic erythropenia	20 (18.5)	5 (20.0)	NA
Haematopoietic leukopenia	16 (14.8)	2 (8.0)	NA
Haematopoietic thrombocytopenia	12 (11.1)	4 (16.0)	NA
Hepatotoxicity (Broad)	39 (36.1)	10 (40.0)	2 (20.0)
Biliary system related investigations, signs and symptoms	23 (21.3)	4 (16.0)	1 (10.0)
Cholestasis and jaundice of hepatic origin	3 (2.8)	1 (4.0)	0
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	6 (5.6)	1 (4.0)	1 (10.0)
Liver related investigations, signs and symptoms	38 (35.2)	10 (40.0)	2 (20.0)
Nephrotoxicity (Broad)	31 (28.7)	8 (32.0)	2 (20.0)
Acute renal failure	31 (28.7)	8 (32.0)	2 (20.0)

Abbreviations: FGFR2=fibroblast growth factor receptor 2.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.
Source: Table 14.3.1.15.1, Table 14.3.1.15.2, Table 14.3.1.15.3

12.5.1. Hepatotoxicity (Broad)

See the primary CSR [X2204p-Section 12.5.1] for a summary of results for hepatoxicity (Broad) in Cohort 1. Results remain generally unchanged since the last report.

Tables further characterizing these minimal toxicities for Cohort 1 are also provided in Tables 14.3.1.25.1 and 14.3.1.33.13.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

Median changes from baseline, Grade 3 and Grade 4 abnormalities, and shifts from baseline for ALT, AST, ALP, and TBL are presented in Section 12.6.2.1.2; results of the drug-induced liver injury (DILI) evaluation are also presented.

Assessment of AEs and laboratory measurements demonstrated no evidence of hepatic toxicity with infigratinib. In total, 2 subjects (1.9%) had AT >3×ULN combined with TBL ≥2.0×ULN and ALP <2×ULN concurrently on the same day (Section 12.6.2.1.2). While the 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.

12.5.2. Cardiac Toxicity (Torsade de Pointes/QT prolongation)

See the primary CSR [X2204p-Section 12.5.2] for a summary of results for cardiac toxicity in Cohort 1. Results remain unchanged since the last report.

Tables further characterizing these minimal toxicities for Cohort 1 are also provided in Tables 14.3.1.27.1 and 14.3.1.33.15.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

Median changes from baseline, Grade 3 and Grade 4 abnormalities, and shifts from baseline in ECG parameters are presented in Section 12.7.2.

AEs and ECGs demonstrated no evidence to suggest that there is any deleterious effect of infigratinib on cardiac function.

12.5.3. Nephrotoxicity

See the primary CSR [X2204p-Section 12.5.3] for a summary of results for nephrotoxicity in Cohort 1. Results remain unchanged since the last report.

Tables further characterizing these minimal toxicities for Cohort 1 are also provided in Tables 14.3.1.29.1 and 14.3.1.33.17.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

Median changes from baseline, Grade 3 and Grade 4 abnormalities, and shifts from baseline in urea nitrogen, uric acid, and creatinine are presented in Section 12.6.2.1.4.

No evidence of renal toxicity was observed.

12.5.4. Hematologic Toxicity

See the primary CSR [X2204p-Section 12.5.4] for a summary of results for hematologic toxicity in Cohort 1. Results remain unchanged since the last report.

Tables further characterizing these minimal toxicities for Cohort 1 are also provided in Tables 14.3.1.31.1 and 14.3.1.33.19.

For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

Based on mechanism of action of infigratinib, the risk of direct hematologic toxicity appears to be low; the observed changes in hematologic values (eg, hemoglobin) were most likely due to anemia of chronic disease and immunosuppression due to underlying disease.

12.6. Clinical Laboratory Evaluation

See the primary CSR [X2204p-Section 14.3.5] for tables and listings supporting clinical laboratory evaluations for subjects in Cohort 1. Results remain generally unchanged since the last report.

For information related to the clinical laboratory evaluation for subjects in Cohort 2 and Cohort 3, see Section 14.3.5 in tables designated as Tables 14.3.5.x for blood chemistry and hematology parameters by analyte, shifts by analyte, postbaseline abnormal results, potential DILI, and shift tables for subjects treated with or without phosphate binders (phosphate binder data available for Cohorts 1 and 2 only). Supporting data are also provided in Figures 14.3.5.13.x and in Section 14.3.4.

12.6.1. Individual Subject Listings

Not provided with this CSR.

12.6.2. Evaluation of Laboratory Parameters

12.6.2.1. Chemistry

See the primary CSR [X2204p-Section 12.6.2.1] for a summary of clinical chemistry evaluations for subjects in Cohort 1. Results remain generally unchanged since the last report with the exception of 1 new report of acute pancreatitis (narrow) for a subject in Cohort 1.

For subjects in Cohort 2 and Cohort 3, summary statistics are presented for absolute values and changes from baseline for the following blood chemistry parameters in Section 14.3.5.2 and Section 14.3.5.3: albumin, potassium, total lipase, magnesium, phosphate, sodium, direct bilirubin, indirect bilirubin, triglycerides, chloride, total protein, ALP, cholesterol, uric acid, ALT, amylase, AST, bilirubin, urea nitrogen, calcium, and creatinine.

Section 14.3.5 also presents data on Cohort 2 and Cohort 3 for subjects with postbaseline blood chemistry abnormalities by grade; with and without grade programmatically defined using CTCAE version 4.03; and shifts from baseline by worst grade in tables designated as Tables 14.3.5.8.x and Tables 14.3.5.9.x (analytes: albumin, total lipase, magnesium, sodium,

triglycerides, cholesterol, urea nitrogen, ALP, ALT, amylase, AST, bilirubin, creatinine, potassium, calcium, and phosphate).

12.6.2.1.1. Calcium and Phosphate

See Section 12.4.1.

12.6.2.1.2. Liver Function Tests and Bilirubin

Median Changes from Baseline

See the primary CSR [X2204p-Section 12.6.2.1.2] for a summary of liver function tests and bilirubin for subjects in Cohort 1. Results remain generally unchanged since the last report.

In Cohort 2, median ALP, ALT, AST, and TBL values at baseline were 176.0 U/L, 24.0 U/L, 38.0 U/L, and 10.6 µmol/L, respectively (Table 14.3.5.2.12, Table 14.3.5.2.23, Table 14.3.5.2.30, Table 14.3.5.2.31). Likewise, median changes from baseline to minimum postbaseline values were 0.0 U/L, -5.0 U/L, -8.0 U/L, and -3.4 µmol/L, respectively, and median changes from baseline to maximum postbaseline values were 85.0 U/L, 27.0 U/L, 24.0 U/L, and 5.1 µmol/L, respectively.

In Cohort 3, median ALP, ALT, AST, and TBL values at baseline were 163.0 U/L, 30.0 U/L, 39.0 U/L, and 10.1 µmol/L, respectively (Table 14.3.5.3.12, Table 14.3.5.3.23, Table 14.3.5.3.30, Table 14.3.5.3.31). Likewise, median changes from baseline to minimum postbaseline values were -2.5 U/L, -6.5 U/L, -6.0 U/L, and -2.9 µmol/L, respectively, and median changes from baseline to maximum postbaseline values were 70.0 U/L, 22.5 U/L, 27.5 U/L, and 4.3 µmol/L, respectively.

Grade 3 and Grade 4 Abnormalities

See the primary CSR [X2204p-Section 12.6.2.1.2] for a summary of liver function tests and bilirubin for subjects in Cohort 1. Results remain generally unchanged since the last report.

In Cohort 2, Grade 3 abnormalities in liver function tests and TBL consisted of high ALP (4 subjects [16.0%]), high ALT [1 subject [(4.0%]), high AST (1 subject [4.0%]), and high TBL (2 subjects [8.0%]) (Table 14.3.5.4.3). No Grade 4 abnormalities were observed.

In Cohort 3, no Grade 3 or Grade 4 abnormalities in liver function tests and TBL were observed (Table 14.3.5.4.5).

Shifts from Baseline

See the primary CSR [X2204p-Section 12.6.2.1.2] for a summary of liver function tests and bilirubin for subjects in Cohort 1. Results remain generally unchanged since the last report.

Cohort 2

All 25 subjects in Cohort 2 had both baseline and postbaseline data for ALP, ALT, AST, and TBL.

- For ALP, 9 subjects (36.0%) had no shift from baseline to their worst postbaseline grade. Four subjects (16.0%) exhibited a shift in ALP from normal, Grade 1, or Grade 2 at baseline to Grade 3 postbaseline; 7 subjects (28.0%) had a shift in ALP

from normal or Grade 1 at baseline to Grade 2 postbaseline, and 4 subjects (16.0%) had a shift in ALP from normal at baseline to Grade 1. In addition, 1 subject (4.0%) had a shift in ALP from Grade 3 at baseline to Grade 2 postbaseline. No subjects had a shift in ALP from normal, Grade 1, or Grade 2 at baseline to Grade 4 postbaseline.

- For ALT, 14 subjects (56.0%) had no shift from baseline to their worst postbaseline grade. One subject (4.0%) exhibited a shift in ALT from normal, Grade 1, or Grade 2 at baseline to Grade 3 postbaseline, and 10 subjects (40.0%) exhibited a shift from normal at baseline to Grade 1 postbaseline. There were no shifts from baseline, Grade 1, or Grade 2 to Grade 4 postbaseline.
- For AST, 11 subjects (44.0%) had no shift from baseline to their worst postbaseline grade. One subject (4.0%) exhibited a shift in AST from normal, Grade 1, or Grade 2 at baseline to Grade 3 postbaseline; 5 subjects (20.0%) exhibited a shift from Grade 1 at baseline to Grade 2 postbaseline; and 8 subjects (32.0%) exhibited a shift from normal at baseline to Grade 1 postbaseline. There were no shifts from baseline, Grade 1, or Grade 2 to Grade 4 postbaseline.
- For TBL, 18 subjects (72.0%) had no shift from baseline to their worst postbaseline grade. Two subjects (8.0%) exhibited a shift in TBL from normal, Grade 1, or Grade 2 at baseline to Grade 3 postbaseline. No subjects had a shift in TBL from normal, Grade 1, or Grade 2 at baseline to Grade 4 postbaseline.

Complete tabulations of shifts in liver function tests for Cohort 2 are provided in Section 14.3.5.8.

Cohort 3

All 10 subjects in Cohort 3 had both baseline and postbaseline data for ALP, ALT, AST and TBL.

- For ALP, 6 subjects had no shift from baseline to their worst postbaseline grade. There were no shifts from normal, Grade 1, or Grade 2 at baseline to Grade 3 or Grade 4 postbaseline.
- For ALT, 6 subjects had no shift from baseline to their worst postbaseline grade. There were no shifts from normal, Grade 1, or Grade 2 at baseline to Grade 3 or Grade 4 postbaseline.
- For AST, 4 subjects had no shift from baseline to their worst postbaseline grade. There were no shifts from normal, Grade 1, or Grade 2 at baseline to Grade 3 or Grade 4 postbaseline.
- For TBL, 8 subjects had no shift from baseline to their worst postbaseline grade. No subjects had a shift in TBL from normal, Grade 1, or Grade 2 at baseline to Grade 3 or Grade 4 postbaseline.

Complete tabulations of shifts in liver function tests for Cohort 3 are provided in Section 14.3.5.9.

Drug-induced Liver Injury Evaluation

Laboratory data were analyzed to determine if there were additional subjects with evidence for potential DILI who were not identified by analyzing AEs related to liver function tests and TBL. Table 13 lists these laboratory parameters and thresholds routinely used to assess liver function and quantify degree of impairment for potential DILI for subjects in all cohorts.

In Cohort 1, only minor differences from those reported in the primary CSR were observed [X2204p Table 44].

In Cohort 2, a total of 7 subjects (28.0%) had at least 1 occurrence of AST or ALT >3×ULN. Of these, 1 subject (Subject 4002027) had an occurrence of ALT >5×ULN and an occurrence of AST >10×ULN. There were no occurrences of AST or ALT >20×ULN. Four subjects (16.0%) had at least 1 occurrence of TBL ≥2×ULN. Two subjects (8.0%) in Cohort 2 had at least 1 occurrence of AST or ALT (AT) >3×ULN combined with TBL ≥2×ULN, and all occurred concurrently on the same day (Subjects 1007002, 4002027, 5008088) (Listing 14.3.4.2). Three subjects (12.0%) had at least 1 occurrence of AT >3×ULN combined with TBL ≥2.0×ULN concurrently on the same day (Subjects 1007002 and4002027) (Listing 14.3.4.2).

In Cohort 3, 5 subjects had a least 1 occurrence of AT >3×ULN (Subjects 4501016, 4505002, 5003040, 5008089, and 8001214) (Listing 14.3.4.3). There were no occurrences of AT ≥3×ULN and TBL ≥2×ULN.

Table 13: Incidence of Potential Drug-Induced Liver Injury

	Cohort 1[a] (N=108) n (%)	Cohort 2[b] (N=25) n (%)	Cohort 3[c] (N=10) n (%)
AST or ALT			
>3×ULN	24 (22.2)	7 (28.0)	5 (50.0)
>5×ULN	9 (8.3)	1 (4.0)	0
>10×ULN	3 (2.8)	1 (4.0)	0
>20×ULN	2 (1.9)	0	0
ALT			
>3×ULN	19 (17.6)	2 (8.0)	2 (20.0)
>5×ULN	7 (6.5)	1 (4.0)	0
>10×ULN	2 (1.9)	0	0
>20×ULN	1 (0.9)	0	0
TBL			
≥2×ULN	10 (9.3)	4 (16.0)	1 (10.0)
ALP			
>1.5×ULN	80 (74.1)	20 (80.0)	7 (70.0)
Elevation of AT and TBL			
AT >3×ULN and TBL ≥2×ULN (same day)	2 (1.9)	2 (8.0)	0
AT >3×ULN and TBL >1.5×ULN (same day)	5 (4.6)	2 (8.0)	0
AT >3×ULN and TBL ≥2×ULN (on treatment)[d]	4 (3.7)	3 (12.0)	0
AT >3×ULN and TBL >1.5×ULN (on treatment)[d]	6 (5.6)	3 (12.0)	0

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; AT=aminotransferase (ALT and/or AST); FGFR=fibroblast growth factor receptor; TBL=total bilirubin; ULN=upper limit of normal.
Note: All the assessments up to last dose of study treatment + 30 days are included if a subject ends study treatment. If a subject is still on study treatment, all the assessments are included.
[a] Cohort 1=Subjects with FGFR2 fusions/rearrangements.
[b] Cohort 2=Subjects with other FGFR alterations.
[c] Cohort 3=Subjects with FGFR2 fusions/rearrangements who received prior treatment with an FGFR inhibitor.
[d] On-treatment abnormalities may have occurred on the same day or on different days.
Source: Table 14.3.5.11.1, Table 14.3.5.11.2, Table 14.3.5.11.3.

Subjects requiring more detailed examination for potential DILI were identified using guidelines presented in the FDA Guidance for Industry Drug-induced Liver Injury (frequently referred to as Hy's Law analysis) (FDA Guidance for Industry 2009).

Plots displaying on-treatment hepatic laboratory abnormalities of postbaseline peak AST, ALT, and AT >3×ULN and TBL ≥2×ULN are presented by cohort in scatter plots. In Cohort 1, only minor differences from those reported in the primary CSR were observed and no cases of DILI have been observed [X2204p-Section 12.6.2.1.2]. See the primary CSR for further details (Figure 14.3.5.13.12).

In Cohort 2, the scatter plot for AT showed 2 subjects with AT >3×ULN and TBL ≥2×ULN while on treatment (Subjects 4002027 and 5008088). Analyses of all factors involved for these 2 subjects indicated that there were no cases of DILI in this cohort. No subjects in Cohort 3 appeared to have potential DILI (Figure 14.3.5.13.13).

Full details on DILI and potential DILI findings for Cohort 2 and Cohort 3 are provided in Section 14.3.4 and Section 14.3.5 in Table 14.3.5.11.2, and in Figures 14.3.5.13.x.

12.6.2.1.3. Lipase and Amylase

See the primary CSR [X2204p-Section 12.6.2.1.3] for a summary of lipase and amylase for subjects in Cohort 1.

For subjects in Cohort 2 and Cohort 3, median lipase values at baseline were 30.0 U/L and 33.0 U/L, respectively. The median change from baseline to the minimum postbaseline value was -3.0 U/L and -6.0 U/L, respectively. The median change from baseline to the maximum postbaseline value was 32 U/L and 22.5 U/L, respectively.

Grade 3 and Grade 4 abnormalities consisted of Grade 3 high lipase in 2 subjects in Cohort 2 (Listing 16.2.7.2) and no subjects in Cohort 3 (Listing 16.2.7.3). Grade 4 high lipase was reported in 1 subject (Cohort 2, Subject 4002027). The abnormalities were not associated with the PT of pancreatitis. Most of the elevations resolved or returned to baseline.

For the 25 subjects in Cohort 2 who had both baseline and postbaseline lipase data, 15 subjects (60.0%) had no shift in lipase from baseline to their worst postbaseline grade. Three subjects exhibited a shift in lipase from normal, Grade 1, or Grade 2 at baseline to Grade 3 postbaseline. One subject exhibited a shift from normal to Grade 4 (Subject 4002027).

For the 10 subjects in Cohort 3 who had 1 both baseline and postbaseline lipase data, 7 subjects did not demonstrate a shift in amylase from baseline to their worst postbaseline grade. One subject exhibited a shift in lipase from normal, Grade 1, or Grade 2 at baseline to Grade 3 postbaseline. No subjects exhibited a shift to Grade 4 postbaseline value. There were very few amylase shifts from baseline to postbaseline; 1 subject had a shift from normal at baseline to Grade 3, and no subjects had a shift in amylase to Grade 4.

Further details on lipase and amylase findings for Cohort 2 and Cohort 3 are provided in Section 14.3.5.

12.6.2.1.4. Renal Parameters

See the primary CSR [X2204p-Section 12.6.2.1.4] for a summary of renal parameters for subjects in Cohort 1.

For subjects in Cohort 2, baseline median uric acid, urea nitrogen, and creatinine values were 296.0 µmol/L, 5.0 mmol/L, and 76.9 µmol/L, respectively. The median change from baseline to the minimum postbaseline value was -23.8 µmol/L, -1.1 mmol/L, and -8.0 µmol/L, respectively (Tables 14.3.5.2.x).

For subjects in Cohort 3, baseline median uric acid, urea nitrogen, and creatinine values were 333.1 µmol/L, 4.6 mmol/L, and 70.7 µmol/L, respectively. The median change from baseline to the minimum postbaseline value was -8.9 µmol/L, 0.0 mmol/L, and -3.1 µmol/L, respectively (Tables 14.3.5.3.x).

For subjects in Cohort 2, Grade 3 abnormalities for clinical chemistry parameters related to nephrotoxicity consisted of high urate (7 subjects [28.0%]) and high creatinine (1 subject [4.0%]).

For subjects in Cohort 3, Grade 3 abnormalities included high urate (4 subjects). There were no Grade 4 abnormalities in clinical chemistry parameters related to nephrotoxicity reported in this cohort.

One of the 25 subjects in Cohort 2 had a shift in creatinine from normal at baseline to worst postbaseline of Grade 3, but none had a change to Grade 4. In Cohort 3, no subject had a shift in creatinine from normal, Grade 1, or Grade 2 at baseline to worst postbaseline of Grade 3 or Grade 4.

In addition, 7 subjects in Cohort 2 had shifts in hyperuricemia from normal at baseline to worst postbaseline values of Grade 3 (6 subjects) or Grade 4 (1 subject) (Table 14.3.5.8.7). In Cohort 3, 2 subjects had shifts in hyperuricemia from normal at baseline to worst postbaseline value of Grade 3 (Table 14.3.5.9.7).

Further details on renal parameters for Cohort 2 and Cohort 3 are provided in Section 14.3.5 in tables designated as Table 14.3.5.2.x; Tables 14.3.5.4.x, Tables 14.3.5.8.x; and Tables 14.3.5.9.x.

12.6.2.1.5. Other Chemistries

See the primary CSR [X2204p-Section 12.6.2.1.5] for a summary of findings for the remaining clinical chemistry parameters for subjects in Cohort 1.

For subjects in Cohort 2 and Cohort 3, median changes from baseline to minimum postbaseline values and to maximum postbaseline values were generally unremarkable for the remaining clinical chemistry parameters.

For Cohort 2, Grade 3 abnormalities for the remaining clinical chemistry parameters consisted of low sodium (5 subject [20.0%]), increased blood bilirubin (2 subjects [80%]), and low potassium (2 subjects [8.0%]). Grade 4 abnormalities consisted of high magnesium (2 subjects [8.0%]) and low calcium, high calcium, and low sodium (1 subject each [4.0%]).

For Cohort 3, Grade 3 abnormalities for the remaining clinical chemistry parameters consisted of low sodium (2 subjects). No Grade 4 abnormalities were reported for the remaining clinical chemistry parameters.

Further details on other clinical chemistry parameters for Cohort 2 and Cohort 3 are provided in Section 14.3.5 in tables designated Tables 14.3.5.4.x, Tables 14.3.5.8.x, and Tables 14.3.5.9.x.

12.6.2.2. Hematology

Summary statistics are presented for absolute values and changes from baseline for the following hematology parameters in Section 14.3.5: hemoglobin, neutrophils, platelets, white blood cell counts, basophils, eosinophils, lymphocytes, monocytes, red blood cell counts, partial thromboplastin time (PTT), prothrombin time, hematocrit, and cancer antigen 19-9.

See the primary CSR [X2204p-Section 12.6.2.2] for a summary of findings for subjects in Cohort 1.

For Cohort 2 and Cohort 3, the hematology parameters, median changes from baseline to minimum postbaseline values and to maximum postbaseline values were generally unremarkable.

The number and percentage of subjects with postbaseline hematology abnormalities by grade are presented in shift tables for Cohort 2 in Table 14.3.5.8.8 through Table 14.3.5.8.14, and for Cohort 3 in Table 14.3.5.9.8 through Table 14.3.5.9.14. Laboratory values were graded programmatically using CTCAE version 4.03, or as otherwise specified in the SAP [X2204p-Appendix 16.1.9].

For Cohort 2, postbaseline Grade 3 abnormalities consisted of anemia (2 subjects [8.0%]) and high hemoglobin (1 subjects [4.0%]) (Table 14.3.5.8.8), and decreased lymphocyte count (4 subjects [16.0%]) (Table 14.3.5.8.13). There were no Grade 4 postbaseline hematology abnormalities observed in Cohort 2. For Cohort 3 there were no Grade 3 postbaseline hematology abnormalities, but 1 subject (10.0%; Subject 5010004) had Grade 4 decreased lymphocyte count postbaseline (Table 14.3.5.9.13).

For additional information related to postbaseline abnormal hematology values by grade, see Section 14.3.5.4. For Cohort 2, hematology values are summarized in Tables 14.3.5.2.15 through Table 14.3.5.2.28. For Cohort 3, hematology values are summarized in Tables 14.3.5.3.15 through Table 14.3.5.2.28.

12.6.3. Pregnancy Outcome Results

No subjects became pregnant during the study.

12.7. Vital Signs, Physical Findings, and Other Observations Related to Safety

12.7.1. Ophthalmology Assessments

See Section 12.4.2.

Results for abnormalities in slit lamp exam, optical coherence tomography, and fundoscopy are summarized by cohort in Section 14.3.6.11.

Intraocular pressure results are summarized by cohort in Section 14.3.6.12. Visual acuity score (logMAR) results are summarized by cohort in Section 14.3.6.13.

12.7.2. ECGs and LVEF

By-subject listings of ECGs and LVEF are presented in Appendix 16.2.8.2 and 16.2.8.4, respectively.

12.7.2.1. LVEF

See the primary CSR [X2204p-Section 12.7.2.1] for a summary of findings for LVEF for subjects in Cohort 1. Results remain unchanged since the last report.

For Cohort 2, 20 of the 25 subjects had postbaseline data, and for Cohort 3, 9 of the 10 subjects had postbaseline data. No shifts from baseline were reported for either cohort.

LVEF results, postbaseline results, and shifts from baseline are summarized by cohort in Section 14.3.6.10.

12.7.2.2. ECG

See the primary CSR [X2204p-Section 12.7.2.2] for a summary of findings for ECG, including changes from baseline summary, shifts from baseline in QTcF and QTcB, and analysis of QT outlier values for subjects in Cohort 1.

For Cohort 2, 11 subjects (45.8%) had one or more postbaseline outlier ECG assessment values. These included:

- New QTcF values >450 msec (4 subjects [16.7%]),
- QTcF change >30 to ≤60 msec (7 subjects [29.2%]),
- New QTcB values >450 msec (4 subjects [16.7%]),
- New QTcB values >480 msec (2 subjects [8.3%]),
- QTcB change >30 to ≤60 msec (4 subjects [16.7]),
- QTcB change >60 msec (1 subject [4.2%]),
- >25% decrease to an HR <50 bpm (2 subjects [8.3%]), and
- >25% increase to an HR >100 bpm (1 subject [4.2%]).

A tabulation of these values is provided in Table 14.3.6.7.7.

For Cohort 3, no postbaseline ECG outlier assessments were reported (Table 14.3.6.8.7).

By-subject listings of ECGs for Cohort 2 and Cohort 3 are provided in Appendix 16.2.8.

12.7.3. Vital Signs

See the primary CSR [X2204p-Section 12.7.3] for a summary of findings for vital signs for subjects in Cohort 1. Results remain generally unchanged since the last report.

For Cohort 2, 4 subjects (16.0%) had increases from baseline pulse of ≥100 bpm (increase of >25%) and 2 subjects (8.0%) had decreases from baseline pulse of ≤50 bpm (decrease of >25%); 3 subjects (12.0%) had decreases from baseline systolic BP to ≤90 mmHg (decrease of ≥20 mmHg); and 4 subjects (16.0%) had decreases from baseline in diastolic BP to ≤50 mmHg (decrease of ≥15 mmHg) (Table 14.3.6.5.2).

For Cohort 3, no abnormal vital signs were reported (Table 14.3.6.5.3).

Vital sign assessments for systolic and diastolic blood pressure, pulse, temperature and weight for Cohort 2 and Cohort 3 are presented in Section 14.3.6 in tables designated as Tables 14.3.6.3.x, and in Table 14.3.6.4.x. Abnormal vital signs are summarized by cohort in Tables 14.3.6.5.x.

12.7.4. ECOG Performance Status

See the primary CSR [X2204p-Section 12.7.4] for a summary of findings for ECOG performance for subjects in Cohort 1. Results remain unchanged since the last report.

Summaries of ECOG performance status by visit are presented by cohort in Section 14.3.6.9.

Changes from baseline in ECOG results for subjects in Cohort 2 and Cohort 3 were generally similar to those observed for Cohort 3. No unexpected ECOG findings were observed.

12.8. Safety Summary

Overall, the safety profile observed in this study was consistent with the expected on-target effects of infigratinib as well as expected adverse events for subjects with cholangiocarcinoma. There were no apparent differences in the safety profile across treatment cohorts; AEs and AESIs were generally the same and as expected. Furthermore, the results observed in Cohort 1, based on last patient, last visit for the study (07 February 2022) were consistent with those reported in the previous CSR [X2204p-Section 12].

- As expected, the median duration of exposure to infigratinib was longer for Cohort 1 (5.6 months [range: 0.03-40.74 months]), relative to Cohort 2 (2.33 months [range: 0.46-29.93 months]), and Cohort 3 (1.63 months [range: 0.69-4.27 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.
- Across the study, nearly all (>99%) subjects had at least 1 AE. The most common PTs in Cohort 1 were hyperphosphatemia (76.9% of all subjects), stomatitis (54.6%), fatigue (40.7%), alopecia (39.8%), dry eye (36.1%), palmar-plantar erythrodysesthesia syndrome (34.3%), arthralgia (32.4%), constipation (31.5%), and dysgeusia (31.5%). The most common PTs reported in Cohort 2 and Cohort 3 were similar to those reported for Cohort 1.
- Grade 3 or Grade 4 AEs were reported in 65.7% of subjects in Cohort 1; 56.5% had at least 1 Grade 3 AE, and 9.3% had at least 1 Grade 4 AE. Stomatitis (14.8%), hyponatremia (13.0%), and hypophosphatemia (13.0%) were the most commonly reported Grade 3 AEs. Grade 4 AEs included sepsis (2.8%) and increased lipase (1.9%). Stress fracture, increased amylase, increased gamma-glutamyltransferase, hypercalcemia, hypophosphatemia, hyperbilirubinemia, and cataract were all reported in 1 subject each (0.9%). The incidence of Grade 3 or Grade 4 AEs in Cohorts 2 (68.0%) and Cohort 3 (60%) was similar to that reported for Cohort 1.
- A total of 119 subjects (83.2%) died during the study, primarily due to study indication (74.1%). Most subjects (76.9%) died during the posttreatment period. For Cohort 1, 93 subjects (86.1%) died during the study: 83 (76.9%) died due to the study indication and 10 (9.3%) died due to other causes. Six of the deaths occurred during the on-treatment period (all due to study indication). For Cohort 2, 19 subjects (76.0%) died during the study: 3 (12%) during the on-treatment period and 16 (64.0%) during posttreatment; most died due to study indication (64.0%). For Cohort 3, 7 subjects (70.0%) died during the study, all due to study indication and all occurring during the posttreatment period.
- In Cohort 1, 35 subjects (32.4%) had at least 1 treatment-emergent SAE, and 9 subjects (8.3%) had an investigator-assessed treatment-related SAE. The most common SAEs (regardless of attribution to study drug) were anemia (3.7%), pyrexia (3.7%), hypercalcemia (3.7%), and sepsis (2.8%). Treatment-emergent SAEs were reported in 11 subjects in

Cohort 2 (with treatment-related SAEs reported in 2 subjects), and in 2 subjects in Cohort 3 (both considered treatment-related).

- A total of 20 subjects (18.5%) in Cohort 1 discontinued study drug due to an AE; events that led to treatment discontinuation in >1 subject were subretinal fluid, fatigue, sepsis, increased aspartate aminotransferase, and increased blood creatinine (1.9% each). Results for Cohort 2 and Cohort 3 were generally similar, with 12.0% and 20.0% of subjects, respectively, discontinuing study treatment due to an AE. In Cohort 2, 3 subjects (12.0%) each had 1 AE that led to treatment discontinuation: visual acuity reduced, peripheral ischemia, and portal vein thrombosis. In Cohort 3, 2 subjects had AEs that led to treatment discontinuation: ascites, stomatitis, pyrexia, enterocolitis infectious, vulvovaginal candidiasis, hypercalcemia, hyperphosphatemia, flank pain, palmar-plantar erythrodysesthesia syndrome (all reported for 1 subject) and reduced visual acuity reported for 1 subject.
- Dose interruption or reduction due to an AE was reported in 66.7% and 60.2% of subjects in Cohort 1, respectively. The most common AE that led to dose interruption or dose reduction was hyperphosphatemia (25.0%, interruption; 25.9%, reduction). Results for Cohort 2 and Cohort 3 were generally similar to that observed for Cohort 1. Dose interruptions due to an AE were reported in 64.0% and 60.0% of subjects in Cohort 2 and Cohort 3, respectively, and dose reductions due to an AE were reported in 36.0% and 40.0%, respectively.
- Nearly all subjects (>95% in each cohort) experienced an AE requiring concomitant medication or non-drug therapy. Across all cohorts, hyperphosphatemia was the most common AE requiring this therapy.
- The incidence of prespecified AESIs in Cohort 1 were generally unchanged from those reported in the primary CSR with the exceptions of 1 new report each of acute pancreatitis and pathological fracture. Detailed results of AESIs are provided in the primary CSR [X2204p – Section 12.4]. For Cohort 2 and Cohort 3, only high-level incidence was provided. Since results were consistent with that reported for Cohort 1 and were as expected for infigratinib, data from these cohorts were not further characterized.
- Assessment of AEs and laboratory measurements demonstrated no evidence of hepatic toxicity with infigratinib. In Cohort 1, 2 subjects (1.9%) had AST or ALT (AT) >3×ULN combined with TBL ≥2.0×ULNIn Cohort 2, 2 subjects (8.0%) 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. While the DILI assessment is never definitive, analyses of all factors involved indicate that there were no cases of DILI.
- For Cohort 1, serious renal events (ie, acute kidney injury) were observed in 1.9% of subjects. For Cohort 2, 1 subject (4.0%) had a shift in creatinine from normal at baseline to worst postbaseline of Grade 3, but none had a change to Grade 4. In Cohort 3, no subject had a shift in creatinine from normal, Grade 1, or Grade 2 at baseline to worst postbaseline of Grade 3 or Grade 4.
- For Cohort 1, subgroup analyses of AEs, AESIs, and minimal toxicity profiles were not conducted for this CSR. Results presented in the interim CSR [X2204i-Section 12.2.3.4, Section 12.8] indicate that profiles were generally similar between demographic subgroups and subgroups related to the use of moderate CYP3A4 inhibitors (vs none), strong CYP3A4

inhibitors (vs none), and strong CYP3A4 inducers (vs none). Overall, no concerning trends were identified. There were not enough Asian subjects, subjects with a body mass index of <18.5 kg/m^2, or subjects who used moderate CYP3A4 inducers to draw meaningful conclusions from these subgroups. For Cohort 2 and Cohort 3, only high-level incidence is provided. Since results were consistent with that expected for infigratinib, data from these cohorts were not further characterized.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1. Discussion

Overall, the safety profile observed in this study was consistent with the expected on-target effects of infigratinib as well as expected adverse events for subjects with cholangiocarcinoma.

Infigratinib at therapeutic doses is associated with disturbances in calcium phosphate homeostasis, based on nonclinical findings. Precautions taken in this study were 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 were related to infigratinib. In Cohort 1, 12.0% of subjects had Grade 3 hyperphosphatemia (there were no Grade 4 events of hyperphosphatemia across any cohort) and 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 adjustment (27.8%), or required concomitant medication or non-drug therapy (67.6%). 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 adjustment, 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 cohorts, hypophosphatemia or 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 or adjustments 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 for 3 of 143 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) of 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. In Cohort 1, 2 subjects (1.9%) had AT >3×ULN combined with TBL ≥2.0×ULN, concurrently on the same day, and no cholestasis (ie, ALP <2×ULN). While the 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.

The safety data from Cohort 2 and Cohort 3 are in line with what is known about infigratinib as previously detailed in the primary CSR. No new safety signals were identified.

There were no apparent differences in the safety profile across treatment cohorts; AEs and AESIs were generally the same and as expected. Furthermore, the results observed in Cohort 1, based on last patient, last visit for the study (07 February 2022) were consistent with that reported in the previous CSR [X2204p-Section 12].

13.2. Conclusions

This abbreviated CSR represents the third and final report of this study. The interim CSR [X2204i] and the primary CSR [X2204p] were the first and second reports, respectively. The initial CSRs reported results from Cohort 1 only, the primary analysis population. This final CSR reports results from all cohorts (Cohorts 1, 2, and 3) of the study.

For the primary analysis population (Cohort 1), a clinically meaningful ORR with durable responses was observed in subjects with advanced or metastatic cholangiocarcinoma. Results for Cohort 1 are further summarized in the primary CSR [X2204p-Section 11.4]. For Cohort 2 and Cohort 3, only limited efficacy was observed; the BOR in the majority of subjects was either stable disease or progressive disease. As a result, the sponsor terminated the study early.

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 subjects, 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.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1. Demographic Data Summary Figures and Tables

14.2. Efficacy Data Summary Figures and Tables [Not applicable]

14.3. Safety Data Summary Figures and Tables

14.3.0 Exposure

14.3.1. Displays of Adverse Events

14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

14.3.4. Listing of Drug-Induced Liver Injury and Potential Hy's Law Cases

14.3.5. Summary of Laboratory Values

14.3.6. Other Safety (Vital Signs, ECG, ECOG PS, LVEF, Ocular)

15. REFERENCES

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16. APPENDICES

16.1. Study Information

16.1.1. Protocol and Protocol Amendments

16.1.2. Sample and Annotated Case Report Form

[X2204i Appendix 16.1.2]

16.1.3. List of IECs and IRBs

[X2204p-Section 16.1.3].

16.1.4. List and Description of Investigators

[X2204p-Section 16.1.4].

16.1.5. Signatures of Principal or Coordinating Investigagtor (s) and/or Sponsor's Responsible Medical Officer

16.1.6. List of Investigational Product(s) Lot Numbers

16.1.7. Randomization Scheme and Codes – Not Applicable

16.1.8. Audit Certificates

[X2204i-Section 16.1.4].

16.1.9. Documentation and Statistical Methods

[X2204p-Section 16.1.9].

16.1.10. Documentation of Inter-Laboratory Standardization Methods and Laboratory Quality Assurance Procedures

[X2204i-Section 16.1.10].

16.1.11. Publications Based on the Study

[X2204i-Section 16.1.11].

16.1.12. Important Publications Referenced in the Report

[X2204i-Section 16.1.12].

16.1.13. Technical Reports

[X2204i-Section 16.1.13].

16.1.14. Charters

[X2204p-Section 16.1.14].

16.2 Subject Data Listings

16.2.1 Disposition, Termination, Follow-up, and Randomization

See Appendix 16.2.4

16.2.3 Subjects Excluded from Efficacy Analysis

[X2204p Appendix 16.2.3]

16.2.4 Disposition Listings

16.2.5 Treatment

16.2.6 Efficacy

16.2.7 Safety

16.2.8 Other Safety (Ophthalmic Examinations, LVEF, ECG)

16.3 Case Report Forms

To be submitted separately.