25 March 2022
EMA/939316/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Febseltiq (WD)

International non-proprietary name: infigratinib

Procedure No. EMEA/H/C/005361/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation/Term	Definition
AE	adverse event
AESI	adverse event of special interest
AUC0-24	area under the concentration-time curve from time 0 to 24 hours
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BOR	best overall response
CCA	cholangiocarcinoma
CI	confidence interval
CLapp	apparent clearance
CMA	conditional marketing authorisation
Cmax	maximum plasma concentration
CR	complete response
CSR/RPED	central serous chorioretinopathy/retinal pigment epithelial detachment
CV	coefficient of variation
DCR	disease control rate
DDI	drug-drug interaction
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E-R	exposure-response
ESCAT	ESMO Scale for Clinical Actionability of molecular Targets
ESMO	European Society of Medical Oncology
FGFR	fibroblast growth factor receptor
GA	genetic aberration
K-M	Kaplan-Meier
LVEF	left ventricular ejection fraction
mFOLFOX	fluorouracil/leucovorin in combination with oxaliplatin
NCI	National Cancer Institute
NGS	Next-generation sequencing
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PFS	progression-free survival
P-gp	p-glycoprotein
PIP	paediatric investigation plan
PK	pharmacokinetics
PR	partial response
QD	once daily
SAE	serious adverse event
SAWP	Scientific Advice Working Party
SD	standard deviation
Tmax	time to maximum concentration
WT	wild type

1. Rapporteur Recommendations

Based on the review of the data on quality, safety, efficacy, the application for **Febseltiq** (**infigratinib)**, an orphan medicinal product applying for the indication

for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

is **not approvable** since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the list of questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality:

- Drug Substance: Re-definition of a starting material.
- Drug Product: Insufficient Dissolution method and its corresponding issue regarding specification and stability of the drug product as well as root cause issue regarding the bioavailability of FMI II.

New active substance status: Information to conclude on the NAS status is insufficient.

Clinical:

- Efficacy has not been established.
- It is unclear if the applied dose results in a manageable safety profile.
- It needs to be justified that the condition of a CMA are fulfilled.
- The indication wording should be adapated.

1.1. Questions to be posed to additional experts

None.

1.2. Inspection issues

1.2.1. GMP inspection(s)

A request for GMP inspection is not required.

1.2.2. GCP inspection(s)

A request for GLP inspection is not required.

1.3. New active substance status

Based on the review of the data, it is currently unclear if the active substance infigratinib phosphate contained in the medicinal product Febseltiq could be qualified as a new active substance.

1.4. Additional data exclusivity /Marketing protection

N/A

1.5. Similarity with authorised orphan medicinal products

It is considered that Febseltiq is not similar to Pemazyre within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000 due to structural differences. Mechanism of action and indication are similar to Pemazyre.

1.6. Derogation(s) from market exclusivity

N/A

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Approval is applied for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

Biliary tract cancers, including intrahepatic and extrahepatic cholangiocarcinoma (CCA) and gallbladder cancers, are tumours characterised by an aggressive disease course and poor clinical outcome. Cholangiocarcinoma is a malignant growth originating in the epithelial lining of the biliary tree that accounts for approximately 3% of all gastrointestinal cancers and approximately 10% of primary liver cancers (Tyson and El-Serag 2011, Bergquist and von Seth 2015, Khan et al 2019). It is commonly classified based on anatomical location; ECC which includes hilar and distal tumours, accounts for the majority of cases, while ICC accounts for less than 10% of cases (DeOliveira et al 2007, Nakeeb et al 1996).

2.1.2. Epidemiology and risk factors, screening tools/prevention

Cholangiocarcinoma is the second most common primary liver tumour worldwide after hepatocellular carcinoma (Blechacz 2017; Khan 2012). In Europe, reported incidence rates range between 0.5/100,000 and 3.4/100,000 (Khan 2019). Over the last few decades, mortality from cholangiocarcinoma has tended to rise in several areas of the world, following the increased prevalence of its major risk factors (Bertuccio 2019).

No predisposing factors are identified in most patients with cholangiocarcinoma, although there is evidence that the presence of chronic inflammation, such as primary sclerosing cholangitis, hepatolithiasis, choledochal cysts, and liver fluke infections, might be associated with the disease in some patients (NCCN 2020). Other risk factors for intrahepatic cholangiocarcinoma have been found to include infections with hepatitis C virus and/or hepatitis B virus, obesity, cirrhosis, diabetes, alcohol, nonalcoholic fatty liver disease, and tobacco use (Welzel 2007).

2.1.3. Biologic features, aetiology and pathogenesis

Genomic characterisation of cholangiocarcinoma has identified potentially actionable molecular alterations that may drive tumourigenesis, including alterations in genes encoding FGFRs that regulate

cell proliferation, survival, migration, and angiogenesis. Comprehensive genomic profiling has identified FGFR2 fusions in approximately 9% to 14% of cholangiocarcinoma patients (Javle et al 2019, Lowery et al 2018).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

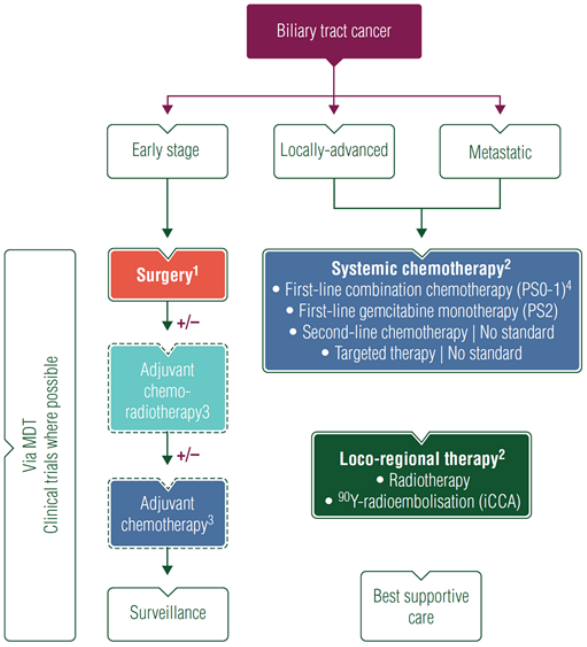
The prognosis for cholangiocarcinoma is generally poor owing to the aggressive nature of the disease, and the late stage at which the disease is typically diagnosed. Cholangiocarcinoma are commonly present at an advanced disease stage with a 5-year survival rate reported to be low and that varies by stage: 50% for stage I, 30% for stage II, 10% for stage III, and 0% for stage IV (Valle et al 2017). The majority of patients with cholangiocarcinoma (> 65%) have nonresectable disease at the time of diagnosis, and the rate of recurrence is high among patients in the minority who are able to undergo potentially curative surgery.

The natural history of CCA with FGFR alterations and its prognostic role is not fully characterised. Retrospective studies have shown that FGFR alterations (predominantly FGFR2 fusions), contrary to the general CCA population, occur more frequently in younger women and seem to confer better prognosis (Graham et al 2014, Churi et al 2014).

2.1.5. Management

Cholangiocarcinoma is a lethal disease for which there is significant unmet need. No agents are approved in the second-line setting. For most patients, palliative chemotherapy is the only treatment option. The first-line, standard-of-care treatment for patients with unresectable and metastatic disease is gemcitabine and cisplatin (ESMO 2016). For second-line treatment, mFOLFOX is recommended based on the ABC-06 trial (Lamarca 2021), which had a progression-free survival (PFS) of 4.0 months and a median OS of 6.2 months, an OS improvement of 0.9 months over best supportive care. Thus, the overall prognosis of patients remains poor with existing methods.

The following algorithm illustrates the management of patients with biliary tract cancer (Valle 2016):



[1] Special considerations:
- Need for pre-operative biliary drainage
- Avoid percutaneous biopsy in resectable disease
- Assess Future Liver Remnant
- Assess need for Portal Vein Embolisation
- Neoadjuvant approach (selected cases)
- Completion surgery for incidental gallbladder cancer of T-stage T1b and above

[2] Option of salvage surgery should be considered in responding patients with initially inoperable disease
[3] Level of recommendation IV,C
[4] Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

For the applied FGFR2 subpopulation, Pemazyre (pemigatinib), a kinase inhibitor targeting FGFR2 fusions or rearrangements has recently received conditional authorisation in the EU for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.

2.2. About the product

Infigratinib is an orally available, potent, selective ATP-competitive inhibitor of fibroblast growth factor receptor (FGFR) 1-3. Kinase selectivity in biochemical assays (IC50) and *in vitro* binding to FGFRs (Kd) are reported different for the subtypes FGFR 1 to 3 (FGFR1 IC50=1.1 nM, Kd=0.53 nM; FGFR2 IC50=1 nM, Kd=1.2 nM and FGFR3 IC50=2 nM, Kd=0.7 nM). It inhibits FGFR phosphorylation and signaling and decreases cell viability in cell lines expressing FGFR genetic alterations, including point mutations, amplifications, and fusions or rearrangements. These genetic alterations in FGFR genes result in activation of FGFR signalling that supports the proliferation and survival of malignant cells.

The proposed indication for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

The recommended dose is 125 mg (one 100 mg capsule and one 25 mg capsule) taken once daily for 21 days followed by 7 days off therapy. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.

2.3. The development programme/compliance with guidance/scientific advice

In relation to quality aspects, scientific advice was given on infigratinib phosphate in October 2019 (EMA/CHMP/SAWP/542686/2019, procedure no.: EMEA/H/SA/4056/2/2019/I). The quality related issues in this scientific advice were the suitability of three proposed starting materials, drug substance test principles and acceptance criteria as well as drug product test principles and acceptance criteria. This advice was followed by the applicant for the most part.

Regarding the nonclinical package, the EMA considered the nonclinical studies as sufficient and adequately performed in accordance with ICH-S9 and deemed that no additional carcinogenicity studies were necessary. The EMA also considered *in vitro* tests to be complete and the planned drug-drug interaction studies reasonable. The waiver in patients with renal impairment was accepted if ADME studies demonstrate less than 10% renal excretion of infigratinib and its metabolites. However, the EMA advised to better characterise elimination pathways and additional analyses were suggested. No issues were raised regarding safety data.

Scientific advice was received from the EMA on 26 April 2019 (EMEA/H/SA/4056/1/2019/III), regarding the possibility to file a conditional marketing authorisation (CMA) based on the data from Phase 2, single-arm Study CBGJ398X2204, for the second and later line treatment of advanced or metastatic cholangiocarcinoma patients with tumours harbouring FGFR2 fusions.

The Scientific Advice Working Party (SAWP) noted the absence of comparator in the ongoing Phase 2 trial and stated this open-label non-controlled Phase 2 trial provides limited data without comparative data to support a CMA application; thus, the demonstration of a positive risk:benefit profile would be at risk due to the possible overestimation of efficacy based on the single-arm nature of the trial, the heterogeneity of the disease, and limited natural history data (specifically as it relates to FGFR2-altered cholangiocarcinoma). In a follow up scientific advice, received on 03 February 2021 (EMA/SA/0000048267), natural history data, including new retrospective data and a comprehensive summary of literature, regarding the prognosis of FGFR-altered cholangiocarcinoma were provided.

However, SAWP concerns with respect to clinical issues were only partially considered, as also acknowledged by the applicant in the clinical overview document.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Qualified Person declaration has been provided by the batch release site to confirm EU GMP compliance of the API manufacturers for Infigratinib for the current synthesis. Updated QP declaration is requested.

Satisfactory manufacturing authorisations has been provided for the drug product manufacturing sites involved in the procedure.

GLP

Pivotal toxicology and safety pharmacology studies as well as validation of bioanalytical methods were generally performed in accordance with Good Laboratory Practice (GLP) in test facilities that were part of an EU or an OECD (Organisation for Economic Cooperation and Development) Mutual Acceptance of Data (MAD) GLP monitoring programme. However, some exceptions were documented. In safety pharmacology studies *0870302* and *0870300*, the system used to record environmental data was under validation and was not fully GLP-compliant. In study *0870300*, the automated ECG analysis software was not GLP-compliant due to pending validation but quality checks were included as a part of the analysis.

Study *0800428* (LC-MS/MS method validation for determination of infigratinib and its metabolites in dog, rat, and human plasma) was GLP-compliant except of inspections by Quality Assurance (QA). However, it is not believed that these deviations might have had an impact on the scientific quality of the study data.

GCP

The applicant states that all clinical trials discussed in this MAA meet the ethical requirements of Directive 2001/20/EC and were performed in compliance with the ICH-GCP including clinical trials conducted outside the European Union.

No GCP inspection is currently recommended.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. PRIME

N/A

2.5.3. Accelerated assessment

Not applied.

2.5.4. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

The applicant is proposing the following confirmatory clinical data to support conversion of the CMA to a full authorisation:

- Follow up data from pivotal Study CBGJ398X2204 Cohort 1 - overall survival and long-term outcomes from previously treated cholangiocarcinoma patients with FGFR2 fusions/rearrangements (expected availability of updated CSR: 2023)

- Confirmatory data from Study QBGJ398-301 with gemcitabine plus cisplatin control arm - safety and efficacy data in previously untreated cholangiocarcinoma patients with FGFR2 fusions/rearrangements (expected CSR availability following primary endpoint: 2027)

Study QBGJ398-301, titled "A Phase 3 Multicenter, Open-Label, Randomized, Controlled Study of Oral Infigratinib Versus Gemcitabine With Cisplatin in Subjects With Advanced/Metastatic or Inoperable Cholangiocarcinoma With FGFR2 Gene Fusions/Translocations: the PROOF Trial," was initiated in 2019.

This multi-centre study intends to enroll approximately 300 subjects in a 2:1 randomisation ratio across 145 study centres worldwide. The primary objective is to determine whether treatment with infigratinib improves PFS as assessed by BICR compared with treatment with gemcitabine and cisplatin in subjects with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions/translocations. Additional objectives will determine whether treatment with infigratinib improves OS compared with treatment with gemcitabine and cisplatin in subjects with unresectable locally

advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions/translocation, and further evaluate the efficacy in subjects treated with infigratinib versus gemcitabine and cisplatin by ORR, BOR, DOR, and disease control rate determined by BICR and by the investigator.

This randomised and controlled study is proposed to serve as a confirmatory study to verify and confirm the clinical benefit of infigratinib in the event that a conditional marketing authorisation is granted based on the Phase 2, single-arm Study CBGJ398X2204.

2.5.5. Marketing authorisation under exceptional circumstances

N/A

2.5.6. Biosimilarity

N/A

2.5.7. Additional data exclusivity/ marketing protection

Not applied.

2.5.8. New active substance status

The applicant requested the active substance (infigratinib) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union. Assessment of this claim is appended.

2.5.9. Orphan designation

The medicinal product "Infigratinib" is designated as an orphan medicinal product for the indication: Treatment of cholangiocarcinoma. (Orphan Medicinal Products EU/3/20/2329).

2.5.10. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report, addressing the possible similarity with the authorised orphan medicinal product Pemazyre. However, non-similarity due to structural differences was assessed, while the indication as well as the mechanism of action was evaluated as similar. Thus, Febseltiq is assessed as non-similar with Pemazyre, the only approved product in the applied indication.

2.5.11. Derogation(s) from orphan market exclusivity

N/A

2.5.12. Information on paediatric requirements

A PIP was submitted on 23 April 2019, requesting a product-specific waiver for cholangiocarcinoma. The procedure EMEA-002594-PIP01-19 started on 28 May 2019, Day 30 comments were received on 02 July 2019, and a product-specific waiver for cholangiocarcinoma was granted on 01 August 2019.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The subject of this centralised application is the drug product Febseltiq, containing infigratinib monophosphate (INN: infigratinib) as the active substance (further stated as "infigratinib phosphate"). Full information on the active substance is provided in Module 3.2.S. There is no reference to an ASMF. A new active substance status is claimed in the EU and a justification for the non-similarity of Infigratinib and pemigatinib is provided (both in same therapeutic class).

The finished product is presented as immediate release hard capsule for oral administration containing Infigratinib phosphate equivalent to 25 and 100 mg Infigratinib free base.

Other ingredients are: lactose monohydrate, microcrystalline cellulose type PH-102, crospovidone type A, hypromellose type 2910, colloidal silicon dioxide, magnesium stearate, gelatin, titanium dioxide, iron oxide, red iron oxide, yellow iron oxide, black iron oxide.

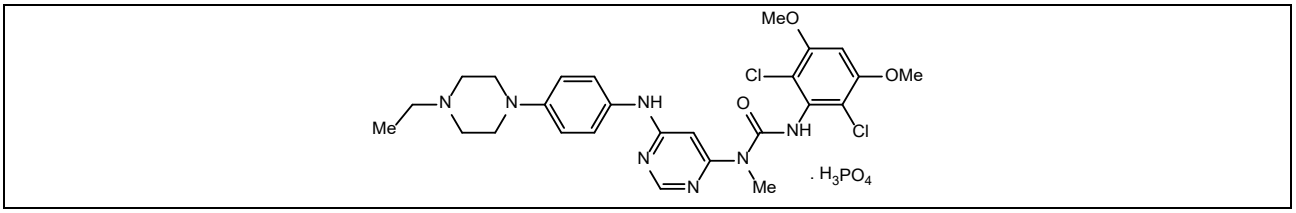
The product is available in PVC/PCTFE/Al blister.

The chemical-pharmaceutical documentation Module 2.3 and 3 is not yet of sufficient quality in view of the present European regulatory requirements.

3.1.2. Active Substance

General Information

Structure, molecular weight and chemical formula are provided as follows:



MW:	560.48 g/mol free base, 658.47 g/mol phosphate salt
Molecular formula:	C26H31Cl2N7O3.H3PO4

General properties have been sufficiently outlined, including solubility characteristics in aqueous and non-aqueous media, polymorphism (only crystalline Form A produced) and thermal properties. The drug substance is achiral and not hygroscopic. Particle size is reduced to NMT 20 µm through milling.

Manufacture, process controls and characterisation

Three sites are involved in manufacture of the active substance. Two sites perform most of the chemical transformation steps.. The third site performs the intermediate step 3 and is located in China. Two further sites are responsible for quality control only. The QP declaration provided by the MIAH site should be signed by MIAH sites located in EEA. Therefore, it should be removed from section B.

The manufacturing process of Infigratinib phosphate includes three defined starting materials:

Synthesis schemes, process flow charts and narrative manufacturing descriptions have been provided including standard quantities or molar equivalents of used raw materials, solvents and reagents as well as pH values, reaction and drying temperatures and times, Operations performed are stated. The commercial batch size is stated and typical yields are provided for each manufacturing step. Reprocessing is not performed. Solvent recovery should be clarified.

The three proposed starting materials are custom synthesised, of high purity and have been determined following EU guidance. However, the number of steps between the proposed starting materials and drug substance is borderline. Following ICH Q11 including Q&A, multiple chemical transformation steps are preferred.

Two of the proposed startindg materials could be approvable if further clarification can be provided and control strategy tightened to mitigate future risks related to short synthesis route.

Control of other raw materials includes the reagents and solvents of each process step.

Regarding critical process parameters and the corresponding process steps, only one temperature related process parameter has been identified as critical. All manufacturing stages are covered by in-process controls.

For each isolated and dried intermediate, information has been provided on specification, control and fate of specified impurities as well as analytical methods. The justification of impurity limits is supported by analytical results and spiking experiments for the most part. However, tightening of total and some single impurity limits and assay limits is requested.

During manufacturing process development, CQAs have been identified and a control strategy has been established. Risk assessments and statistical design of experiments were used to support traditional drug development. Criticality assessments are provided for each process step, listing NORs and PARs and defining CPPs. Design spaces are not claimed. Investigations on polymorphism, crystallisation and solvent retention in the drug substance as well as hydrolysis have been outlined

Infigratinib phosphate has been sufficiently characterised and acceptable IR, UV, NMR (1H, 13C, COSY, HSQC, HMBC) and single crystal XRD data and spectra including interpretation are provided. Mass spectra are presented with fragmentation patterns. Thorough XRPD, DSC, TGA and DVS analysis was performed for investigation of physicochemical properties including the melting point, hygroscopicity and crystal form. Particle size distribution data are provided.

Thorough descriptions of potential impurities as well as their formation, fate and control have been provided, assigned to the respective synthesis steps/intermediates. These impurities comprise starting materials and intermediates including impurities derived thereof, reagents, solvents, potential reaction by-products and potential degradation products. All these impurities are controlled in the respective starting materials, the intermediates or the final drug substance, respectively. Limits for control are backed by spiking/purging experiments. Further clarification on one by-product is requested and further possible degradation pathways should be discussed.

Satisfactory information has been given on nitrosamines. Based on a risk assessment, no additional controls or monitoring of elemental impurities is required for Infigratinib phosphate drug substance.

Regarding residual solvents, satisfactory justification has been given for only testing residues in the drug substance specification (other solvents tested in intermediates).

Specification, analytical procedures, reference standards, batch analysis, and container closure

In general, the specification set is in compliance with relevant regulatory requirements. Identification is performed by IR, HPLC and by XRPD (polymorphic form). The residual solvents are controlled by HS-GC. Further justification for the limit is requested. Related substances can be generally controlled by the used HPLC method. Stability of particle size should be shown to justify the exclusion from stability specifications. Moreover, the applicant has provided satisfactory justification for not including additional tests for elemental impurities and microbial purity in the specification.

Analytical methods for the test parameters identity, assay and related substances (HPLC) as well as residual solvents (HS-GC), phosphate content (IC) and particle size distribution (laser diffraction) have been described in detail including system suitability tests. Further brief descriptions should be provided for the analytical methods used for water content and polymorphic form.

Summarised validation data provided for the described analytical methods are in accordance with the requirements of the relevant ICH guidelines. Validation of the HPLC method for determination of assay and impurities of Infigratinib phosphate should be further detailed . Brief verification data are available for the method for water content determination and should be provided for the methods used for identity (FTIR), solid form/polymorphism (XRPD) and elemental impurities (ICP-MS).

The drug substance specification and batch-to-batch consistency are confirmed by the analysis results of batches manufactured by the commercial process and in the commercial batch size. However, as two From the manufacturing sites proposed, it should be specified at which site the presented batches have been manufactured. Batch data from each site is expected.

Reference standards and container closure system

Qualification of the primary reference standards is considered appropriate.

Stability

Stability data according to the ICH guidelines are presented for a number of batches at commercial scale stored at 25°C±2°C/60% RH±5% RH and stored at 40°C±2°C/75% RH±5% RH. The test results are within the specified limits at all storage conditions.

In addition, a photostability study has been conducted in accordance with ICH Q1b Option 1. The proposed re-test period for Infigratinib phosphate drug substance is considered acceptable based on the stability data and extrapolation of real time data in conjunction with statistical analysis. The drug substance is proposed to be stored up to 25°C.

If the drug substance is intended to be stored refrigerated, in-line with ICH Q1A, long-term stability data at 5°C ± 3°C (including XRPD and PSD) should be provided.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Infigratinib hard capsules contain infigratinib phosphate as active substance, equivalent to 25 mg and 100 mg infigratinib free base.

The 25 mg strength drug product is a size 3 hard gelatin capsule having a white opaque body with grey opaque cap, imprinted with INFI 25mg in black text on the body.

The 100 mg strength drug product is a size 1 hard gelatin capsule having a white opaque body with light orange opaque cap, imprinted with INFI 100mg in black text on the body.

The composition of the drug product is satisfactorily described.

Composition of printing ink: black iron oxide, butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, shellac, strong ammonia solution.

The applicant claims differently in the dossier that infigratinib is a BCS class II or IV substance. However, based on information presented, infigratinib should be classified as a BCS class IV substance. Clarification regarding the classification is requested in the clinical part.

The excipients used are standard and commonly used in the pharmaceutical industry. Infigratinib monophosphate is compatible with all excipients used. The development of the formulation has been described in detail with focus on the formulations developed during clinical development and the commercial process.

The different formulations have been described in detail; all batches used in the clinical and pharmaceutical studies have been listed. The clinical assessor has an issue regarding the stability of the clinical batches, as the packaging system is bottles instead of blister.

Infinigranib 25 and 100 mg capsules manufacturing process uses a conventional process. For the manufacturing transfer, a risk assessment has been performed.

The manufacturing process of the final formulation has been further optimised as well as manufacturing process.

The development of dissolution method has been described. The dissolution media chosen, the apparatus used, and speed are discussed. The discriminatory power of the dissolution method has not been shown as discussed in detail hereafter. The discriminatory ability of the dissolution method was studied by deliberate changes to composition or by deliberate changes to the manufacturing process . Indeed, the figures where dissolution results of the development formulations are compared, show that the dissolution profiles of CSF, FMI II, FMI III and FMI IV have similar dissolution profiles, although one of the formulations led to a different exposure in comparison to the other formulations. Thus, the proposed dissolution method is apparently not able to identify batches with unacceptable bioavailability. A new dissolution method must be proposed.

Due to the nature of the dissolution method, and considering that the drug release is a critical quality attribute, no conclusions can be drawn regarding drug release based on the manufacturing process development studies.

The container closure system used is a standard container for capsules.

Manufacture of the product and process controls

A flowchart of all activities and responsibilities of the manufacturing sites is outlined in Module 1 Annex 5.8. Copies of manufacturing authorisations and GMP compliance have been attached in Module 1 Annexe 5.6 and 5.9.

Infigratinib drug product is currently formulated as hard capsules (25 and 100 mg). The batch formulas provided are in accordance with the composition documented in P.1.

The manufacturing process and the stability performance of the formulation do not require the use of an overage.

The description includes conditions/parameters used, IPCs, and equipment used.

As the dissolution method has been shown non-discriminatory, the proposed PARs need further justification and data should be presented.

Results of manufacturing process validation are not presented for this standard method of manufacture, which can be considered acceptable. Results of several batches used in the clinical and stability studies have been presented and details of the manufacturing process . Nevertheless, the validation protocols need to be updated.

The applicant declares that continued process verification (CPV) will be performed on the entire Infigratinib FMI IV commercial drug product manufacturing and packaging process to monitor and optimise performance. As the manufacturing process is a standard process, this is acceptable.

Excipients

All excipients used in manufacturing of infigratinib capsules are standard excipient in manufacturing of hard capsule and of compendial (Ph. Eur.) grade and will be tested according to the current edition of the Ph. Eur. except of the capsule shells. The compounds of the capsule shell, gelatin and titanium dioxide, are specified according to Ph. Eur. The quality of red iron oxide and black iron oxide are controlled according to the USP/NF and EU 231/2012 requirements. The specification of the capsule shell is sufficient.

Based on the information provided in P.2 and the CoAs presented, some specific functional parameters have been additionally specified by the manufacturer of the final medicinal product or the supplier of the excipients. These specifications should be adequately addressed in section P.4.1.

Sufficient information about BSE/TSE risk of the excipients have been provided. For gelatin sufficient CEPs have been presented.

Product specification, analytical procedures, batch analysis

The specifications contain tests typically used to control such products as per CPMP/ICH/367/96 Specification: Test procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

Some proposed limits (for release and shelf-life) are above the qualification limit. Presented information on the qualification is not considered sufficient - further clarifications are needed in order to determine suitable limits.

The acceptance criterion defined for assay is in line with the requirements defined in the Annex I of the EU Directive 2001/83, as amended but not the shelf-life specification.

All analytical procedures used for drug testing at release and shelf life have been well described. The validation data submitted are in accordance with the requirements of the relevant ICH guidelines and are therefore mainly accepted. However, questions have been raised regarding the analytical method/analytical validation for some parameters.

The methods used for assay and impurities are stability indicating.

Furthermore, validation data of some parameters could not be located.

The batch analyses data demonstrate batch-to-batch consistency; no out-of-specification results have been reported. However, it should be considered that batch results of the deviating early development formulations batches has not been presented.

A risk evaluation on elemental impurities has been performed according to ICH Q3D guideline and a summary has been presented. Based on the information provided below, the total elemental impurity

level from all sources in the drug product is expected to be consistently less than 30% of the permitted daily exposure (PDE), therefore no additional controls such as including elemental impurity testing in the release testing of the drug product is required.

A sufficient nitrosamine risk assessment has been performed.

For the reference standards, reference is made to S.5.

The applied primary packaging system is standard for solid oral formulations. The provided specifications and information for the proposed container closure systems are considered otherwise sufficient, however, identification of the materials used for primary packaging should be included to the specifications of the container closure system for commercial supply.

No information on the packaging system of bulk ware have been presented.

Stability of the product

The stability studies have been performed in line with ICH Q1A on a number of baches packed in representative packaging and manufactured at the proposed site of manufacture using drug substance from proposed manufacturer.

Due to the incapability of the method to detect batches , no shelf-life for drug product can be accepted based on the results. The results need to be evaluated against acceptable limits.

The applicant listed different storage conditions in module 1, 2.3 and 3, this should be corrected. Nevertheless, further evaluation regarding suitable storage temperature should be made on additional data of ongoing stability study.

The results obtained from the photo-stability study show that the drug product is photo-stable.

Hold time study is completed for capsules. No bulk hold times can be accepted.

Results of the ongoing stability studies should be submitted. The above questions on the specifications should be considered.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Regarding the drug substance, the centralised application is not approvable as a major objection has been identified in relation to a starting material. In addition, sufficient information should be given to the other concerns according to the list of questions.

Information on development, manufacture and control of finished product have been presented in a satisfactory manner with some major exception regarding the dissolution method and its corresponding issue regarding the specification and stability/shelf-life for which the root cause need to be clarified in order to set up suitable control measures to guarantee batch-to-batch consistency.

Besides the major objections regarding the dissolution problem and root cause issue regarding bioavailability there were a number of minor unresolved quality issues having no impact on the benefit-risk balance of the product.

3.2. Non-clinical aspects

3.2.1. Introduction

Infigratinib (formerly BGJ398) is an oral, potent adenosine triphosphate (ATP)-competitive small molecule inhibitor of fibroblast growth factor receptor (FGFR)1-3. Infigratinib is proposed as monotherapy for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

FGFR fusions are the result of gene rearrangements and have been detected in different types of human cancers, including cholangiocarcinoma. FGFR fusion partners generally contain dimerisation or oligomerisation domains that facilitate ligand-independent activation of the receptor and downstream mitogen-activated protein kinases (MAPK) / extracellular signal regulated kinase (ERK) and janus kinase (JAK)/ signal transducer and activator of transcription (STAT) signalling pathways. Particularly, FGFR2 fusions with different partners have been detected in approximately 15% to 20% of intrahepatic cholangiocarcinomas and shown to be the oncogenic driver in these tumours. Therefore, FGFR2 fusions in cholangiocarcinoma, which is a serious and life-threatening disease with limited treatment options and overall poor prognosis, represent a potential target for a potent and selective FGFR inhibitor.

The non-clinical programme has been designed according to ICH (International Council for Harmonisation) S9 guideline on non-clinical evaluation of anticancer pharmaceuticals and ICH M3 (R2) on non-clinical safety studies.

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

No definite information was provided by the applicant where and how binding of infigratinib occurs and what the result of binding is: e.g., binding at the extracellular domain(s) in competition to physiological ligand as a receptor antagonist; binding at the intracellular site(s) for auto-phosphorylation, for ATP, in the kinase domain; whether conformational changes are expected. This is considered missing relevant data and should be submitted.

Infigratinib demonstrated high affinity for FGFR1-3 (with exception of FGFR3(V555M)) and lower affinity for FGFR4 in biochemical and cellular assays. The binding constant Kd of infigratinib to FGFR1-3 varied between 0.5 and 10 nM, whereas it was 65 nM for FGFR3(V555M) and 29 nM for FGFR4. The human metabolites of infigratinib BHS697 and CQM157 and a metabolite BQR917 detected in non-clinical studies exhibited similar affinity towards FGFRs. These results correlated with the data on inhibition of FGFR phosphorylation by infigratinib obtained using a capture ELISA assay (the IC_{50} values for FGFR1-3 varied between 4.3 and 5.6 nM and was 164 nM for FGFR4). These results were supported by the data from a kinase profiling assay showing that IC_{50} was 1.1, 1.0 and 2.0 nM for FGFR1, FGFR2 and FGFR3, respectively, and 61 nM for FGFR4. The lowest IC_{50} for non-FGFR kinases was observed for KDR (210 nM).

Infigratinib inhibited proliferation of bladder carcinoma cells dependent on WT FGFR3 activity, multiple myeloma cells dependent on mutated FGFR3, breast cancer cells with sustained FGFR2 overexpression, acute myeloid leukaemia cell line with FGFR1-OP2 fusion and Ba/F3 cells overexpressing FGFR1 with BCR or ZNF198 fusion with the IC_{50} values in the range 1.7 – 55 nM. Cell lines overexpressing FGFR4 (MDA-MB453 breast carcinoma and HUH7 hepatocellular carcinoma) were less sensitive showing IC_{50} of 255 and 100 nM. In the case of the HUH7 cell line, the contribution of FGFR3 is possible since FGFR3 was also highly expressed in these cells. Generally, FGFR inhibition by infigratinib triggered inhibition of the

phosphorylation of the downstream targets STAT3/5 (for FGFR1) and FRS2 (other FGFRs). The applicant found a correlation between the levels of p-FRS2 in cell lines and their sensitivity to infigratinib and suggests that phospho-FRS2 could possibly be used as a biomarker to select patient populations with constitutive FGFR signalling and thus with potential to respond to FGFR inhibitors. Although a (not quantified) correlation is noted, using p-FRS2 as a biomarker would need a more thorough validation. Taken together, the data show anti-tumour activity of infigratinib in various cell lines. Cholangiocarcinoma cells were not studied to support the non-clinical development in the proposed indication. This is considered a missing important part of the non-clinical proof-of-principle.

The potential of the metabolite BHS697 to inhibit phosphorylation of FGFR1, FGRF2 and FGFR3 was ca. 3-fold lower compared to the parent drug. The inhibitory potential towards FGFR4 was comparable between infigratinib and BHS697. The anti-proliferatory effects of the metabolite and the parent drug were similar in cells dependent on FGFR2-4. The activity of BHS697 in LN427 glioblastoma cells could not be compared to that of infigratinib because the study report with the respective data (presumably RD-2007-01140) had not been provided. Evaluation of the major human metabolite CQM157 in cellular assays is missing.

Infigratinib displayed significant inhibition of tumour growth in MGHU3 bladder carcinoma mouse xenograft model featuring mutant FGFR3(Y373C) with 4 out of 10 animals being complete responders. In AN3CA endometrial cancer xenografts overexpressing FGFR2 in rats and mice, dose-dependent significant tumour growth inhibition up to 0.6% of the control tumour volume in rats and to 3.5% in mice was observed. It was noted that the title of section 3.5 and the title of Table 8.2 in study report RD-2009-00471 mentions RT112 cells but the assessor assumes this to be a typing mistake. In the WT FGFR3-dependent RT112 bladder carcinoma rat xenograft model, tumour growth was reduced to 2% of the initial volume at the highest dose of 15 mg/kg. At 10 and 15 mg/kg, a dose-dependent increase in FGF23 levels in serum and plasma was found. At these doses characterised by a significant anti-tumour response, mineralisation of tissues was noted. The initial accumulation of the drug was observed in kidneys, lung and stomach, but was cleared quickly.

Preliminary PK/PD studies demonstrated that the inhibition of FGFR-mediated signalling by infigratinib in tumours matched the PK profile, with strong inhibition at the early time points and slow recovery with time correlating with compound elimination from the tumour tissue. Similar correlation was observed for the metabolite BHS697. Both the metabolite and the parent compound distributed into tumour tissue (tumour-to-plasma ratio varied between 6 and 22) but to a much higher extent into liver (31- to 39-fold higher exposure compared to plasma). Although the compound was rather quickly cleared, it still remained in liver at 24 h. In another study, BHS697 accumulated in liver and in kidneys to a great extent with the tissue/plasma ratios of 54 and 64, respectively. The metabolite still remained in these tissues after 24 h. The applicant is invited to discuss the clinical relevance of these findings. The metabolite BQR917 quickly converted to BHS697 after administration to tumour-bearing mice. Therefore, the observed pharmacodynamic response was attributed to BHS697.

The *in vivo* activity of infigratinib was also evaluated in cholangiocarcinoma patient-derived xenografts. In CTG-0997 mouse model, tumour regression was observed at doses ≥ 20 mg/kg/day. There were only 2 partial responders (tumour volume ≤ 30% of tumour volume at day 0 for 2 consecutive measurements) in the 40 mg/kg group and one partial responder in the 60 mg/kg group (out of five animals per group).

In the CC6702 mouse model, infigratinib significantly reduced tumour growth at 30 and 50 mg/kg/day. However, after the last dose tumour growth inhibition was reversible. Given that only partial response was detected in the CTG-0997 model and no *in vitro* or ex vivo pharmacodynamic data are available for cholangiocarcinoma, the applicant is asked to justify the non-clinical proof-of-principle for the proposed indication in relation to the clinical data.

3.2.2.2. Secondary pharmacodynamic studies

Infigratinib displayed broad off-target activity having the highest affinity for 5HT2A receptor and histamine H3 receptor with IC_{50} of 260 and 440 nM, respectively. These values are more than 18-fold higher than the unbound clinical Cmax of 14.2 nM calculated by the assessor based on the data in Summary of Clinical Pharmacology (Cmax = 248.7 ng/mL, M = 560.48 g/mol, fu = 3.2%). Given the much lower clinical plasma concentration and no off-target-related effects in non-clinical studies, the above-mentioned off-target interactions appear not to be clinically relevant.

BHS697 also had a broad off-target activity profile, with the most prominent targets being LCK and Lyn kinases with IC_{50} of 94 and 120 nM in a kinase activity assay, and μ-opioid peptide receptor and hERG potassium channel with IC_{50} of 1 and 1.1 μM in binding assays. These interactions are not likely to be clinically relevant given the unbound clinical Cmax of 0.91 nM calculated by the assessor based on the data in Summary of Clinical Pharmacology (Cmax = 37.26 ng/mL, M = 532.43 g/mol, fu = 1.3%).

CQM157 showed little off-target activity with the highest affinity towards 5HT2A and 5HT2B receptors having IC_{50} of 1.2 and 1.4 μM. The clinical relevance of these interactions appears very unlikely taking into account the unbound clinical Cmax of 0.2 nM calculated by the assessor based on the data in Summary of Clinical Pharmacology (Cmax = 19.03 ng/mL, M = 463.32 g/mol, fu = 0.5%).

It was noted that in study FR095-0014250, Nr. 100050669 the data is presented only for 60 of the 430 kinases available in the assay. The applicant is requested to provide the missing data.

3.2.2.3. Safety pharmacology programme

In GLP-compliant studies, infigratinib, BHS697, and CQM157 inhibited hERG current with the IC_{50} values of 2.0, 1.2, and 2.7 μM. These concentrations are 140, 1318 and 13500 fold higher than the respective unbound clinical Cmax (as calculated above). The clinical relevance of the hERG inhibition is therefore very unlikely. Furthermore, no infigratinib-related effects on ECG, heart rate, arterial blood pressure or core body temperature were noted in male Beagle dogs up to 200 mg/kg, but vomiting was observed at this dose level. Infigratinib did not impact nervous system as evaluated by Functional Observational Battery and respiratory parameters (tidal volume, respiratory rate, minute volume) of Wistar rats at 10 mg/kg.

3.2.2.4. Pharmacodynamic drug interactions

Co-administration of phosphate binder did not influence the pharmacokinetics of infigratinib. Unexpectedly, mineralisation of tissues was aggravated upon combination with phosphate binder. No other pharmacodynamic drug interaction studies were conducted. This is acceptable since infigratinib is proposed to be used as monotherapy.

3.2.3. Pharmacokinetics

The bioanalytical methods to be used in pharmacokinetic and toxicokinetic studies were developed and successfully validated. Method validation in study *0800428* including *0800428a* and *0800428b* was performed under GLP conditions except QA inspections. It is, however, not believed that conducting QA inspections under non-GLP conditions might have had any scientifically significant impact on the results of the method validation study. It is noted that in the aforementioned study the bias for BQR917 in the validation of the dilution linearity in dog plasma exceeded 24% and it has not been discussed by the applicant. The acceptance criteria for the stability of incurred samples in dog and rat plasma were set at ±30% deviation of the nominal value, which is wider than recommended by the EMA guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2. The applicant is asked to justify.

The absorption of infigratinib was investigated after intravenous and oral administration to healthy rats, dogs and monkeys. The pharmacokinetic profile of the metabolites BHS697, BQR917 and CQM157 was also characterised.

After intravenous dosing of infigratinib in rats, dogs and monkeys, Cmax was reached within 0.5 h. The pharmacokinetics was characterised by high volume of distribution and slow clearance in all three species. Following oral administration of infigratinib to rats, dogs and monkeys, the absorption was slow. In all three species, a major first-pass effect was observed. The oral bioavailability was moderate in rodents (17.1%) and low in non-rodents (2.39% in dogs and 1.5-1.6% in monkeys). It was noted that in both monkey studies, plasma concentrations could only be measured at some time points after oral administration, with the majority of data being under LLOQ. In general, large variability was observed between individual animals. Since monkey is not a pivotal toxicological species and the data in monkeys can be at most regarded as supportive, this issue will not be further pursued. In many studies, the acceptance criteria for QC samples in bioanalytical measurements were set at ±30% deviation of the nominal value, which is wider than recommended by the EMA guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2. This issue is, however, not further pursued because the actual deviation in the bioanalytical runs did not exceed ±15% specified in the EMA guideline.

In rats, the exposure of the metabolites BHS697 and BQR917 was similar to that of the parent drug. In dogs, BQR917 had a much higher exposure than the parent, BHS697 and CQM157 were characterised by a slightly higher exposure. However, the data for BHS697 are variable between studies. In monkeys, BHS697 exposure appears to be much higher after oral dosing and much lower after i.v. administration as compared to the parent drug. This is a puzzling observation but as mentioned above the data in monkeys are supportive at best and therefore, no further discussion is needed.

Infigratinib and its metabolites BHS697 and CQM157 were highly protein bound across species (>95%). In human, infigratinib was highly bound to lipoproteins. Protein binding of BHS697 and CQM157 in dog plasma was not evaluated. The applicant is requested to justify. The metabolite BQR917 showed extensive protein binding in human, rabbit and rat plasma (>94%) and moderate binding in mouse and dog (around 85%).

In mouse, rat, dog and human blood, infigratinib did not preferentially distribute into erythrocytes with plasma fractions varying between 42% (mouse) and 76% (dog, human).

In vivo distribution of infigratinib was investigated in rats after intravenous and oral administration of the ^{14}C-labelled drug. The labelling positions are adequate. The parent drug and/or its metabolites were extensively distributed into the tissues, passed the blood-brain barrier, and were specifically taken up into the melanin-containing structures in a partly reversible manner. Infigratinib and BQR917 were quickly cleared from brain, which was not the case for BHS697. Both infigratinib and BHS697 had a broad off-target affinity profile. Given much higher IC_{50} values than the unbound clinical Cmax in human plasma the applicant concluded that the off-target interactions appear to be not clinically relevant (see Pharmacology section). The applicant should further discuss the unbound fraction of infigratinib and the metabolites in brain tissue environment compared to protein binding in plasma and assess risk of adverse effects following off-target activity.

Infigratinib is extensively bound to melanin and very high concentrations of radioactivity were measured in melanin-containing eye tissues of rats. Concentrations of total radioactivity were still measurable 2520 hours postdose for 3 melanin-containing tissues/matrices (eye choroid, eye ciliary body, and meninges). Detailed discussion of risk for ocular adverse effects in patients due to high binding of infigratinib to melanin-containing eye tissues should be provided.

In rat, dog and human hepatocytes, N-oxidation and N-deethylation metabolic reactions were observed. The formation of the N-oxide M1 (BQR917) was predominant in dog hepatocytes, whereas the N-deethylation yielding M3 (BHS697) was a main biotransformation in rat and human hepatocytes. Rat and monkey hepatocytes metabolised infigratinib to a low extent. In rat hepatocytes, the major metabolite was M9 (glutathione conjugation), whereas in incubates from monkey hepatocytes M3 (BHS697; *N*-deethylation) and M25 (*C*-hydroxylation) were quantified in major amounts. In pooled human liver microsomes, the major metabolic pathways of infigratinib were N-deethylation to M3 (BHS697), O-demethylation to M7 and N-oxidation to M1 (BQR917). Infigratinib was metabolised by recombinant human CYP3A4 (to M3 and M7), CYP3A5 (to M3), FMO1 and FMO3 (to N-oxide M1). CYP3A4/5 were the major enzymes involved in the oxidative metabolism of infigratinib with partial contribution by FMO (6%).

In animal models, mainly oxidative metabolism was observed. In rats, the major primary biotransformation seems to be *N*-oxidation (M1 = BQR917), followed in importance by *C*-hydroxylation (M25, which is also a possible precursor of the carboxylic acid formation M22) and *N*-deethylation (M3 = BHS697). In the intestine, M1 (BQR917) was totally reduced to BGJ398 indicating the possibility of an enterohepatic circulation. Also in dogs, infigratinib was mainly eliminated unchanged, possibly as a result of the complete reduction of M1. The major primary biotransformations in dogs were *N*-deethylation (M3 = BHS697) and the formation of the carboxylic acid M22, followed in importance by *C*-hydroxylation (M25, possible precursor of the carboxylic acid M22). In monkeys, oxidative metabolism also played a major role. In plasma, the unchanged drug was the predominant component followed by M1, M25 and M3. The metabolite M22 was the most abundant component in both faeces and urine of monkeys.

Infigratinib was almost exclusively excreted via faeces in intact animals, with renal elimination contributing not more than 6.5%. In bile-duct cannulated rats, the proportion of biliary excretion was 56.6% indicating major elimination via bile. It was noted that the total recovery of radioactivity in monkeys in study *1000668* was rather low. The applicant is requested to comment.

In vitro studies of CYP enzyme inhibition by infigratinib identified inhibitory potential of the compound for CYP2C9, CYP2C19 and CYP3A4/5, with K_i values ranging from 0.234 μM to 5.43 μM. For CYP3A4/5, a very weak time-dependent (irreversible) inhibition was observed. *In vivo* evaluation of the DDI potential is warranted only for CYP3A4/5. *In vitro* data did not suggest possible *in vivo* relevance for any of the other enzymes studied (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1). BHS697 demonstrated inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 with K_i in the range 4.2 μM to 24 μM. However, the *in vivo* relevance of these effects is unlikely. CQM157 inhibited CYP2C enzymes and CYP3A4/5 (K_i values lay between 3.1 μM to 9.6 μM). These interactions are not likely to be relevant for the clinical situation. Infigratinib did not activate the pregnane X receptor (PXR) and did not induce CYP1A2, CYP2B6, CYP2C9 and CYP3A4. BHS697 did not induce PXR and AhR (the aryl hydrocarbon receptor). Little data on the DDI potential of BQR917 is available. This is acceptable as BQR917 is a minor human metabolite.

In vitro studies showed that infigratinib is likely a substrate of P-gp and BCRP. It was not investigated whether infigratinib is a substrate of MATE1 and MATE2-K but this is acceptable given a low contribution of renal excretion to the elimination of the drug. CQM157 is likely to be a substrate of P-gp and BCRP in contrast to BHS687. BQR917 is a likely an OATP1B1/3 substrate. Infigratinib was found to inhibit BCRP and MATE1 *in vitro* to an extent warranting *in vivo* studies. The applicant does indeed specify that the *in vivo* relevance of these inhibitory effects cannot be excluded. However, the applicant did not conduct any *in vivo* study to investigate the clinical relevance of BCRP and MATE1 inhibition by infigratinib as recommended by the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**). BHS697 and CQM157 did not inhibit transporters to an extent, which may be clinically relevant. No data is available on the potential of BQR917 for transporter inhibition but this is acceptable as BQR917 is a minor human metabolite.

3.2.4. Toxicology

The non-clinical toxicological profile of infigratinib and two major human metabolites (BHS697 and CQM157) has been characterised through single- and repeat-dose toxicity studies up to 26 or 39-weeks in rats and dogs, respectively. The oral QD dosing in animals was consistent with the intended clinical route of administration.

3.2.4.1. Single dose toxicity

Single dose toxicity studies with infigratinib have been conducted in rats and dogs. Infigratinib was tolerated in female rats after single oral doses up to 2000 mg/kg using a formulation containing 1% carboxymethyl cellulose. The applicant often uses the term BGJ398 as abbreviation for infigratinib. Thus, it is unclear what the term BGJ398**-C5** means as it is written in the original study report 0507847. The applicant is requested to clarify.

Infigratinib was also tolerated in male and female dogs following oral escalating doses up to 300 mg/kg. TK parameters were analysed but a definitive conclusion about the data are not possible due to the limited sample size (1 animal/sex/dose). The study protocol is named "summary report". This might be not the original study protocol. Please provide the original study protocol or justify the submission of the summary report.

In both studies, the free base form of infigratinib was used which is in contrast to the intended clinical form (phosphate form). Further, PEG300 was included in the final formulation for the single-dose toxicity studies which is also not included in the final commercial form. The applicant is requested to comment on this.

3.2.4.2. Repeat dose toxicity

Non-pivotal repeat-dose toxicity studies have been conducted in rats and dogs for up to two weeks. However, both high-dosed animal groups (rat: 20 mg/kg, dogs: 300 mg/kg) had to be euthanised early due to poor condition of the animals. Prominent target organ in rats was the hematopoietic system together with adverse effects relating to changes in homeostasis. In dogs calcification was the most prominent adverse effect. Effects related to this change in homeostasis included tissue mineralisation as well as changes in eye, heart, GI tract, kidneys, lungs, mesentery, and/or brain. TK analysis was included in the dog study. However, no real conclusion can be drawn from the data because only 1 animal/sex/dose was included and there were distinct gender differences, e.g. the 30 mg/kg/day dose corresponds to a mean Cmax and AUC0-24h of 69.2 ng/mL and 682 ng*h/mL, respectively after 14 days of dosing. The mean AUC value of 69.2 ng/mL based on 34.4 ng/mL for the male animal and 104 ng/mL for the female animal.

It is stated that the free base form of infigratinib was used for the 2-week oral exploratory rat study but the vehicle was titled "not specified". Please explain the meaning of "not specified".

Pivotal repeat-dose toxicity studies were conducted in rats and dogs up to 26- and 39-weeks, respectively. Within these studies the biomarker fibroblast growth factor FGF23 was analysed. FGF23 is a pharmacodynamics marker in the context of inhibition of FGF-Rs since loss of FGF23 activity is thought to lead to increased phosphate levels. The determination of FGF23 was performed using a validated ELISA. However, the validation report is missing (*Study No. 1370451, Assay Validation of FGF23 ELISA in Rat, Dog, Mouse and NHP; report in preparation*) and should be provided.

Following administration of infigratinib, remarkable findings were attributed to the intended pharmacology of infigratinib (FGFR inhibition). The main target organ was bone followed by changes in calcium/phosphorus homeostasis. Hyperphosphataemia resulted in ectopic tissue mineralisation in

multiple tissues including kidneys, GI tract, lungs, mesenteric, and/or brain, aorta, heart, blood vessels and changes in the cornea (eye). Infigratinib-related effects in the brain of rats demonstrated that the drug crosses the blood-brain-barrier (BBB).

Hyperphosphataemia has also been observed as an on-target pharmacologic effect of FGFR inhibition in clinical studies and is categorised as a serious adverse event.

Ectopic tissue mineralisation was observed in kidneys in rats after administration of 10 mg/kg for 4 weeks and ≥3 mg/kg for 13 weeks and in dogs after administration of 300 mg/kg after 7 days of dosing and at 30 mg/kg after 14 days of dosing. These changes were partially or full reversible after a 4- or 6-week recovery period.

In an oral exploratory toxicity study in rats the potential of infigratinib on tissue mineralisation after repeated administration and different recovery phases was determined as well as clinical pathological biomarkers that might indicate the risk for mineralisation. Administration of 10 mg/kg/day for 15 days or 20 mg/kg/day for up to 6 days resulted in morphological changes in blood vessels including aorta (vasculopathy with degeneration and mineralisation), lungs, (multifocal alveolar septae thickening with or without presence of mineralisation) kidneys (tubular basophilia) and bones (femur/tibia/sternum growth plate thickening and femur/tibia/patella bone changes). Vascular changes comprised degeneration and mineralisation in large blood vessels and in vessels of different organs, such as the heart, GI-tract, kidneys and lung. Bone changes occurred down to the dose-level of 10 mg/kg/day. The findings showed a tendency to reversibility in all affected organs or were reversible after the different recovery periods, e.g. for the bone. However, ectopic mineralisation was not recoverable. A second study was conducted in order to test the hypothesis if the observed ectopic mineralisation may be secondary to changes in phosphor/calcium metabolism similarly as observed with renal insufficiency. Animals were fed a diet containing the phosphate binder sevelamer prior and during administration of infigratinib. Administration of 20 mg/kg/day infigratinib to male rats for 3 or 7 days resulted in ectopic calcification and severe toxicity in multiple organs. Recovery ranged from no to full recovery. The co-administration of the phosphate binder sevelamer did not reduced the toxic effects but resulted in an increase. Thus, the hypothesis that ectopic calcification could be the result of higher phosphate levels could not be proved.

Corneal opacities were observed in the 4-and 13-week rat study at a dose ≥3 mg/kg. The severity increased with dose and correlated microscopically with keratopathy and corneal mineralisation with partial (4-week recovery) to full reversibility (6-week recovery). Further evaluation of the corneal opacities in different rat strains (Wistar and Brown Norway) for up to 4 weeks led to the conclusion that corneal opacities and related microscopic findings were not rat strain specific but the result of the FGFR inhibition through infigratinib. This assumption is underlined by the fact that all four FGFR genes are expressed in the lens, and FGFR1 and FGFR2 are expressed in the retina and cornea, and thus, may have contributed to observed exacerbation of corneal crystals. The NOAEL for corneal toxicity was identified as 3 mg/kg/day following 26-weeks of infigratinib administration.

Adverse effects on bones, microscopic and bone quality parameters were observed in femur, tibia, lumbar vertebral bodies and/or sternum in rats and dogs after 26- or 39-weeks of treatment. In rats, bone toxicities were present ≥3 mg/kg/day resulting in growth plate thickening of femur and sternum, decreased thickness epithelium of the hard palate and at the dose of 10 mg/kg/day cartilage hypertrophy of the nasal cavity was found. Further, within the 26-week repeat-dose toxicity study in rats decreases in total bone mineral density of femur and decreases in bone strength at the lumbar vertebral body (L4 and L5) in males at ≥ 1 mg/kg/day, the latter was partially reversible during the recovery period. Evaluation of the bone density showed an alteration of the relationship between bone mass and strength in the vertebral bodies (0.57 to 0.86; statistically significant for controls and

males at 1 mg/kg) indicating that infigratinib affects the bone quality. This finding is underlined by the decrease in total bone mineral density and may result in fractures in humans.

Microscopic bone effects in dogs at ≥1 mg/kg/day included growth plate thickening in the sternum in repeat-dose studies up to 13 weeks in duration and changes in the rib costo-chondal junction. These bone changes were partially reversible. After 39 weeks of dosing in dogs, microscopic findings in the lumbar vertebrae consisted of retention of portions of growth plate within vertebral bodies (i.e., increased thickness of the growth plate) and fractures in the retained growth plates. These findings correlated with radiographic findings of increased physeal thickness, focal mixed reaction, and/or bone loss in both sexes at 3 mg/kg/day. Findings fully reversed by the end of the 13-week recovery period.

Different dosing formulations were used in repeat-dose toxicity studies in dogs. In 13-week and 39-week studies a formulation containing a mixture of 0.1 M acetic acid/acetate buffer pH 4.68 and PEG300 (50/50%) was used. In contrast, in 4-week study a formulation containing 0.5% HPMC 100 T was used. It is unclear what caused the GI-related changes such as loss appetite and liquid faces in 13-week study. However, in GLP embryo-fetal development study in rabbits morbidity/mortality was observed in the control group and all infigratinib-treated groups (0.3, 1, and 3 mg/kg/day) at a similar incidence and was indicative of potential tolerability issues related to the vehicle (0.1 M acetate buffer, pH 4.6, and PEG300). There should be some discussion about tolerability issues related to the same vehicle used in 13-week study in dogs.

Bone-derived fibroblast growth factor-23 (FGF23) plays an important role in systemic phosphate turnover. Increased FGF23 activity results in hypophosphatemic, while reduced activity is linked to hyperphosphatemic disorders. FGF23, together with klotho as co-factor, can activate FGF-receptors in its target tissues to exert its functions. Thus, it is assumed that the observed bone toxicities could be probably attributed to the inhibition of one or more FGFRs by infigratinib.

Teeth dysplasia (degeneration of ameloblast epithelium and an absence of enamel) in rats were observed at 10 mg/kg/day in the 13-week repeat dose toxicity study. These abnormalities are considered pharmacology-driven as they were observed in nonclinical studies performed with other FGFR inhibitors. Physeal findings observed in rats are considered likely of low risk to adult patients where growth plates are closed. Rats used in toxicology studies are still rapidly growing at initiation of these studies. Similarly, the tooth findings in rats are considered not relevant to adult patients, as the incisors grow continuously in rats. Further changes of the epithelium of the tongue and vascular endothelial cells of the oral mucosa observed in the 13-week repeat-dose toxicity study in rats dosed 10 mg/kg/day were attributed to the pharmacological action of infigratinib. Administration of 10 mg/kg/day infigratinib over 13-weeks in rats and dogs resulted in changes in coat appearance, acinar atrophy of the dorsal sebaceous glands and/or hyperkeratosis of the inguinal skin. It is assumed that these changes were the result of the FGFR inhibition. The NOAEL for the effects on epithelial tissues, teeth, and skin/hair was 3 mg/kg/day in rats in rats following 26-weeks of treatment and also 3 mg/kg/day in dogs following 39 weeks of treatment.

Fully reversible mild-to-moderate elevation of ALT and AST were noted at the end of the dosing period in the 13-week rat study up to 10 mg/kg/day and in the 4- and 13-week dog study at 10 mg/kg/day. These changes were not associated with changes in other hepatobiliary parameters or microscopic changes in the liver. The NOAELs for the effects on the liver were 3 mg/kg/day in rats following 26-weeks of treatment and also 3 mg/kg/day in dogs following 39 weeks of treatment.

The major human metabolites BHS697 and CQM157, were pharmacologically active in rats and dogs. However, the PK parameters of the metabolite BQR917 (N-oxide metabolite of infigratinib) were disproportionally higher than that of infigratinib and the two major human metabolites. However, since the metabolite BQR917 was not identified in a human ADME study, this might not be of clinical relevance.

Mortality was observed in repeat-dose toxicity studies at 20 mg/kg/day for rats and 300 mg/kg/day for dogs. However, this difference may be explained by poor oral absorption of infigratinib in dogs. In 13-week dog study, at the highest dose, 10 mg/kg/day the combined AUCng*hr/mL of infigratinib on Day 78 was 0.05-fold compared to human steady-steady AUCng*hr/mL at clinical dose 125 QD and in 39-week dog study at the highest dose, 3 mg/kg/day the combined AUCng*hr/mL of infigratinib on Day 273 was 0.03-fold compared to human AUCng*hr/mL of infigratinib on Day 15 at clinical dose 125 QD. In 39-week study in dogs, the AUCng*hr/mL of the main metabolite BHS697 on Day 273 was 0.14-fold compared to human steady-steady AUCng*hr/mL of BHS697 on Day 15 at clinical dose 125 QD. Considering the lack of safety margins in pivotal toxicity studies in dogs, the applicant is asked to discuss the overall clinical relevance of safety findings in this toxicological species.

3.2.4.3. Genotoxicity

Infigratinib was negative in an i*n vitro* Ames and in a mammalian cell mutation test in human peripheral blood lymphocytes with and without metabolic activation (± S9). *In vivo* infigratinib was negative for clastogenic effects in a chromosome aberration test (rat, micronuclei in bone marrow cells). Due to a lack of appropriate TK data (60 mg/d), a safety margin to the clinical exposure could not be calculated. Based on the TK data available for rat all safety margins were calculated < 1 up to 20 mg/kg/d.

The metabolite BHS697 was determined not to be mutagenic based on DEREK and SARAH prediction.

The metabolite CQM17 was determined not to be mutagenic based on DEREK and inconclusive based on SARAH prediction. Due to several limitation (u. a. a miniscreen Ames test and only the Salmonella strains TA98 and TA100 were used without justification, detailed study data and historical control data were not provided with the study report) the Miniscreen Ames test was not acceptable and therefore, the study did to support a negative outcome for mutagenicity of CQM17. Nevertheless, since the intended indication falls into the scope of ICHS9 no further studies to evaluate the genotoxicity of the metabolite CQM17 are necessary.

In conclusion, infigratinib did not exert any genotoxic potential based on the studies performed. The lack of a safety margin in the *in vivo* micronucleus test should be mentioned in section 5.3 of the SPC.

3.2.4.4. Carcinogenicity

The indication of the application falls into the scope of ICHS9 and thus no carcinogenicity studies are necessary.

3.2.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity

A complete programme of reproductive and developmental toxicity studies has been performed with infigratinib, including studies on fertility and early embryonic development in rats, dose-range-findings and definitive embryo-foetal developmental studies in rats and rabbits and a pre- and postnatal developmental study in rats. The studies have been performed in accordance with ICH S5 (R3) guideline. The pivotal studies were conducted under GLP regulation.

Febseltiq is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma and falls into the scope of the ICH S9 guideline. Therefore, the majority of the reproductive and developmental studies conducted with infigratinib are not necessarily warranted for the proposed indication in advanced cancer, as are the fertility and early embryonic developmental study in rats, the embryo-foetal developmental study in rabbits and the pre-postnatal developmental

study in rats. Furthermore, in all reproductive and developmental toxicity studies exposures of infigratinib and its major metabolites were only far below the human exposure at the recommended human dose.

Infigratinib-related embryo-foetal toxicity and lethality were observed in all reproductive and developmental toxicity studies in rats and/or rabbits. Furthermore, external, visceral, and skeletal morphologic abnormalities were observed in the embryo-foetal developmental study in rats. FGF ligands and FGFRs are widely expressed during development, and FGF-FGFR signalling is essential during embryonic development. Therefore, based on the mechanism of action of infigratinib (inhibitor of FGFR1-3), the effects on embryo-foetal development seen in the reproductive and developmental toxicity studies should be regarded as relevant for humans and infigratinib should be classified as a suspected human teratogen.

Infigratinib has no effects on mating or fertility, reproductive organ weights, or sperm motility, density, or morphology in male rats, and no effect on oestrous cycling, mating or fertility in female rats at dose levels of up to 3 mg/kg/day. Since the estimated exposure in the study at 3 mg/kg/day is expected to be only far below the human exposure at the RHD, the study has some limitations for investigating the impact on fertility in relation to the clinical exposure. Literature data suggest a role of FGFs and FGFRs in spermatogenesis and folliculogenesis and thus a potential for impacting fertility.

Infigratinib, when administered during the pre-postnatal period to rats, had no effects on development and fertility of the F1 generation, except for a decrease in premating body weight gain and food consumption in F1 females. However, the relevance of the study is limited due to the insufficient exposures levels compared to the human exposure at the recommended human dose especially with regard to the no observed effects.

A few deficiencies have been observed in some studies. These include insufficient historical control data provided for the fertility and early embryonic development study and the dose range finding study on embryo-foetal development in rats. Furthermore difficulties in interpretation of the study results occurred due to potential toxicity of the vehicle used in the embryo-foetal developmental study in rabbits. However, the overall conclusion regarding effects of infigratinib on reproduction and development is not impacted by these findings and therefore, these deficiencies are not further addressed.

There are no data on the placental transfer of infigratinib and/or its major human metabolites and the potential exposure to the foetus, but the teratogenic findings in rats suggest that infigratinib and/or its metabolites are transferred to the foetus. Furthermore, there are no data on the transfer of infigratinib and/or its major human metabolites into semen or into breast-milk. Therefore, the potential risk to the embryo or foetus via semen exposure and the potential risk to the suckling child via breast-milk exposure is unknown but cannot be excluded.

A time period of 1 month after end of treatment with infigratinib for use of effective contraception in male and females and for the discontinuation of breast-feeding is proposed in the product information. A justification should be provided by the applicant.

Juvenile toxicity studies are not required based on the current patient population and no studies have been submitted by the applicant. However, a juvenile toxicity study with infigratinib is mentioned (Study No. 20163480) in the study reports of the DRF-EFD studies in rats and rabbits which provides the basis for the dose levels used in these studies. This study should be submitted.

3.2.4.6. Toxicokinetic data

As the applicant summarises in the Nonclinical Overview, "the safety margins at all dose levels in all studies was <1 based on a comparison of Cmax or AUC values in rat and dog toxicity studies to the

human exposure (5364 ng*hr/mL; Cycle 1, Day 15) at the recommended dose of 125 mg QD, reflecting the greater sensitivity of the species used in the nonclinical toxicology programme to the pharmacologic effects (ie, inhibition of FGFR1-3) of infigratinib."

The following text is proposed to be added in section 5.3 of the SmPC:

The highest plasma exposures achieved in the repeat-dose toxicology studies were associated with significant toxicity, including mortality, and were below the tolerated plasma exposures in patients at the highest recommended dose of 125 mg QD, suggesting humans are less sensitive than preclinical species to the toxicities of infigratinib. Clinically relevant exposures were not attained in the species used in the toxicology studies, therefore these studies have a limited value in producing clinically relevant safety data on infigratinib.

3.2.4.7. Tolerance

Infigratinib was evaluated for local tolerance in a skin and an ocular irritation assay in rabbits. The results demonstrated that infigratinib is not recognised as a skin irritant but produced reversible conjunctivitis. Therefore, according to the Kay and Calandra Evaluation Criteria, infigratinib was considered to be a mild irritant to ocular tissues in rabbits and according to the EEC Ocular Evaluation Criteria, infigratinib was classified as a non-irritant.

3.2.4.8. Other toxicity studies

Phototoxicity

Distribution studies in partly pigmented rats showed that infigratinib was distributed to the eyes (choroid, ciliary body) with high affinity for melanin. The maximum absorption of infigratinib was observed at 294 and 310 nm with molar extinction coefficients (MEC) of about 37.18 and 40.88 M^{-1} cm^{-1}. According to the current guideline ICHS10 "Photosafety Evaluation of Pharmaceuticals" (2014), photosafety testing is not requested, since both MECs were well below 1000 M^{-1} cm^{-1}. Together with the fact that infigratinib was photostable in a photostability test in accordance with ICHQ1B, infigratinib is not anticipated to be phototoxic in humans.

3.2.5. Ecotoxicity/environmental risk assessment

An ERA Phase I for the active ingredient infigratinib was provided. Based on treatment regimen as described in the SmPC and on prevalence data taken from Orphanet and publicly available literature, Fpen was refined. The resulting $PEC_{surface\ water}$ of 0.0014 µg/l does not exceed the action limit and the applicant concluded that Phase II testing is not triggered. Further PBT assessment has not been considered since the experimentally derived log D_{ow} of 3.2 (pH 7) does not exceed the trigger value of 4.5.

The Fpen refinement cannot be supported since the prevalence used for refinement is only estimated and thus not comprehensible to the assessor. However, according to the document on orphan designation (EU/3/20/2329) Cholangiocarcinoma affected approximately 1.7 in 10,000 people in the European Union (EU) at the time of designation. Based on this information a Fpen of 0.00013 can be derived and a $PEC_{surface\ water}$ of 0.008 µg/l calculated, respectively. As the resulting $PEC_{surface\ water}$ of 0.008 µg/l does not exceed the action limit of 0.01 µg/l, the ERA can stop in Phase I and a Phase II ERA is deemed not necessary.

As within the environmentally relevant pH-range, i.e. at pH 9 log D_{ow} of 4.8 exceeds the action limit of 4.5 the applicant's conclusion for not providing a PBT assessment cannot be followed. Therefore, the

applicant is asked to perform a screening for persistence, bioaccumulation and toxicity for the active ingredient infigratinib as required by the respective guidelines.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of infigratinib to the environment.

Summary of main study results

Substance (INN/Invented Name): Infigratinib			
CAS-number (if available): 1310746-10-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OECD107	at pH 5: 1.7 at pH 7: 3.2 **at pH 9: 4.8**	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	at pH 9: 4.8	potentially B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (based on prevalence and treatment regimen)	0.008	µg/L	> 0.01 threshold (N)

3.2.6. Discussion on non-clinical aspects

In **Pharmacology** section, no information was provided on the mode of infigratinib binding (e.g. binding site, binding consequences). This is considered missing relevant data and should be submitted.

In vitro, infigratinib demonstrated high affinity for FGFR1-3 and lower affinity for FGFR4 in biochemical and cellular assays. Infigratinib inhibited proliferation of various cells dependent on FGFR1-3 activity, with IC_{50} values in the low nanomolar range. However, cholangiocarcinoma cell lines were not studied to support the non-clinical development in the proposed indication. This is considered a missing important part of the non-clinical proof-of-principle. The anti-proliferatory effects of the metabolite and the parent drug were similar in cells dependent on FGFR2-4. The activity of BHS697 in LN427 glioblastoma cells could not be compared to that of infigratinib because the study report with the respective data (presumably RD-2007-01140) had not been provided. Evaluation of the major human metabolite CQM157 in cellular assays is missing.

In vivo, infigratinib demonstrated significant inhibition of tumour growth in several mouse xenograft models overexpressing FGFRs. In CTG-0997 cholangiocarcinoma patient-derived xenografts, tumour regression was observed at doses ≥ 20 mg/kg/day. There were only 2 partial responders in the 40 mg/kg group and one partial responder in the 60 mg/kg group (out of five animals per group). In the CC6702 mouse model, infigratinib significantly reduced tumour growth at 30 and 50 mg/kg/day. However, after the last dose tumour growth inhibition was reversible. Given that only partial response was detected in CTG-0997 model and no *in vitro* or ex vivo pharmacodynamic data are available for cholangiocarcinoma, the applicant is asked to justify the non-clinical proof-of-principle for the proposed indication in relation to the clinical data. Both infigratinib and BHS697 distributed into tumour tissue but to a much higher

extent into liver (more than 30 fold higher exposure compared to plasma). Infigratinib still remained in liver at 24 h. BHS697 accumulated in liver and in kidneys to a great extent and remained in these tissues after 24 h. The applicant is invited to discuss the clinical relevance of these findings.

Infigratinib and BHS697 exhibited broad **off-target activity** that is not likely to be clinically relevant given the much lower clinical plasma concentration and no off-target-related effects in non-clinical studies. CQM157 had little off-target activity. It was noted that in study FR095-0014250, Nr. 100050669, the data is presented only for 60 of the 430 kinases available in the assay. The applicant is requested to provide missing data.

The bioanalytical methods to be used in pharmacokinetic and toxicokinetic studies were developed and successfully validated. It is noted that in study *0800428* the bias for BQR917 in the validation of the dilution linearity in dog plasma exceeds 24% and it has not been discussed by the applicant. The acceptance criteria for the stability of incurred samples in dog and rat plasma were set at ±30% deviation of the nominal value, which is wider than recommended by the EMA guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2. This should be justified.

The absorption of infigratinib was investigated after intravenous and oral administration to healthy rats, dogs and monkeys. In both monkey studies, plasma concentrations could only be measured at several time points after oral administration, and the majority of data was under LLOQ. In general, large variability was observed between individual animals. The observation that BHS697 exposure was much higher after oral dosing and much lower after i.v. administration as compared to the parent drug is puzzling. However, as monkey is not a pivotal toxicological species and the data in monkeys can be at most considered supportive, these issues will not be further pursued.

Infigratinib and its metabolites BHS697 and CQM157 were highly protein bound across species (>95%). Protein binding of BHS697 and CQM157 in dog plasma was not evaluated. The applicant is asked to justify.

***In vivo* distribution** of infigratinib was investigated in rats after intravenous and oral administration of the ^{14}C-labelled drug. The parent drug and/or its metabolites were extensively distributed into the tissues, passed the blood-brain barrier, and were specifically taken up into the melanin-containing structures in a partly reversible manner. Infigratinib and BQR917 were quickly cleared from brain, unlike BHS697. Both infigratinib and BHS697 had a broad off-target affinity profile. Given much higher IC_{50} values than the unbound clinical Cmax in human plasma the applicant concluded that the off-target interactions appear to be not clinically relevant (see Pharmacology section). The applicant should further discuss the unbound fraction of infigratinin and the metabolites in brain tissue environment compared to protein binding in plasma and assess risk of adverse effects following off-target activity.

Infigratinib is extensively bound to melanin and very high concentrations of radioactivity were measured in melanin-containing eye tissues of rats. Concentrations of total radioactivity were still measurable 2520 hours postdose for 3 melanin-containing tissues/matrices (eye choroid, eye ciliary body, and meninges). Detailed discussion of risk for ocular adverse effects in patients due to high binding of infigratinib to melanin-containing eye tissues should be provided.

In hepatocytes and animal models, mainly **oxidative metabolism** was observed. In rats, the major primary biotransformations were *N*-oxidation to BQR917 and *N*-deethylation to BHS697. In the intestine, BQR917 was totally reduced to BGJ398 indicating the possibility of an enterohepatic circulation. Infigratinib was almost exclusively excreted via faeces in intact animals, with renal elimination contributing not more than 6.5%. It was noted that the total recovery of radioactivity in monkeys in study *1000668* was rather low. The applicant is requested to comment.

In vitro studies of CYP enzyme inhibition indicated that *in vivo* evaluation of the **DDI potential** was warranted only for CYP3A4/5. *In vitro* studies showed that infigratinib is likely a substrate of P-gp and

BCRP. Infigratinib was found to inhibit BCRP and MATE1 *in vitro* to an extent warranting *in vivo* studies. The applicant does indeed specify that the *in vivo* relevance of these inhibitory effects cannot be excluded. However, the applicant did not conduct any *in vivo* study to investigate the clinical relevance of BCRP and MATE1 inhibition by infigratinib as recommended by the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**).

Single-dose toxicity studies with infigratinib (free base) have been conducted in male rats and dogs. Administration of infigratinib p.o. was tolerated up to the highest dose tested, with more adverse effects observed in dogs compared to rats. TK parameters were analysed in dogs. However, due to the sample size of one animal/dose, the results can only be regarded as supportive. The protocol provided for the dog study (report 0510122) is titled summary report. If there exists a full study report, the applicant is invited to provide this. Further, it is not clear whether the term BGJ398-C5 used in the rat study is identical with BGJ398 or not.

Non-pivotal repeat-dose toxicity studies were performed with rats and dogs up to 2-weeks duration. Both studies were early terminated (rats: after 7th administration, dogs: after 8th administration) due to poor condition of the animals. The main target organ in rats was the hematopoietic system ($\geq$ 6 mg/kg/day) and in dogs gallbladder and bone marrow ($\geq$30 mg/kg). Treatment-related changes on calcium metabolism resulted in ectopic tissue/organ mineralisation (heart, GI tract, kidneys, lungs, mesentery, and/or brain) and changes in the eye of rats and dogs. There is an inconsistency of the vehicle form on infigratinib in the rat study. The term „not specified" should be clarified. PK parameters were analysed in both studies. However, due to the sample size of one animal/sex/dose, the results can only be regarded as supportive. Further, the protocol provided for the rat study (report 0510121) is titled summary report. If there exists a full study report, the applicant is invited to provide this.

In the pivotal repeat-dose toxicity studies the most prominent findings following administration of infigratinib in both rats and dogs were attributed to the intended pharmacology of infigratinib as FGFR1-3 inhibitor, including hyperphosphataemia, physeal dysplasia, and soft tissue mineralisation. Mineralisation was observed in numerous tissues including kidneys, stomach, arteries (gastric and pulmonary), and eyes (cornea; rat only). Infigratinib-related effects in the brain of rats demonstrated that the drug crosses the blood-brain-barrier (BBB). Corneal opacity and eye-related microscopic findings were not rat strain specific and appeared to be related to the pharmacologic mechanism (inhibition of FGFR1-3) of infigratinib. Ectopic calcification was found not to be the result of the higher phosphate levels since the administration of the phosphate binder sevelamer did not reduce this finding.

Different dosing formulations were used in repeat-dose toxicity studies in dogs. In 13-week and 39-week studies a formulation containing a mixture of 0.1 M acetic acid/acetate buffer pH 4.68 and PEG300 (50/50%) was used. In contrast, in 4-week study a formulation containing 0.5% HPMC 100 T was used. It is unclear what caused the GI-related changes such as loss appetite and liquid faces in 13-week study. However, in GLP embryo-fetal development study in rabbits morbidity/mortality was observed in the control group and all infigratinib-treated groups (0.3, 1, and 3 mg/kg/day) at a similar incidence and was indicative of potential tolerability issues related to the vehicle (0.1 M acetate buffer, pH 4.6, and PEG300). There should be some discussion about tolerability issues related to the same vehicle used in 13-week study in dogs.

In summary, the infigratinib toxicology programme followed the appropriate ICH guidelines S9 and M3(R2). The pivotal studies were conducted in compliance with GLP with the exception of the FGF23 determination. The data provided demonstrated that administration of infigratinib to rats and dogs resulted in a number of adverse effects. One predominant effect was the change in calcium/phosphorus homeostasis with ectopic tissue mineralisation in multiple tissues and in large and small blood vessels as well as changes in the eye including increases in corneal opacities and keratopathy. The primary effect on homeostasis and subsequent tissue changes were attributed to the pharmacological mechanism of

action of infigratinib as inhibitor of FGF1-3. But since ocular toxicity and hyperphosphataemia were also present in the clinical setting, special emphasis should be laid on these topics in humans. Ectopic mineralisation in kidney and lung was observed in the 4- and 13-week rat (3 mg/kg/day) and the 4-week dog (10 mg/kg/day) studies with recovery dependent on the dosage. The kidney mineralisation was accompanied with electrolyte and protein changes. Changes in bones including decrease of bone strength, decrease in total bone mineral density (BMD) of femur and decreases in bone strength at the lumbar vertebral body were another important adverse effect observed in rats and dogs following 26- or 39-weeks of treatment at ≥1 or 3 mg/kg/day, respectively with partial or full recovery after the recovery period. However, bone effects were also observed in humans which could resulted in uncontrolled fractures. Thus, BMD should be monitored in the clinical setting.

Mortality was observed in repeat-dose toxicity studies at 20 mg/kg/day for rats and 300 mg/kg/day for dogs. However, this difference may be explained by poor oral absorption of infigratinib in dogs. In 13-week dog study, at the highest dose, 10 mg/kg/day the combined AUCng*hr/mL of infigratinib on Day 78 was 0.05-fold compared to human steady-steady AUCng*hr/mL at clinical dose 125 QD and in 39-week dog study at the highest dose, 3 mg/kg/day the combined AUCng*hr/mL of infigratinib on Day 273 was 0.03-fold compared to human AUCng*hr/mL of infigratinib on Day 15 at clinical dose 125 QD. In 39-week study in dogs, the AUCng*hr/mL of the main metabolite BHS697 on Day 273 was 0.14-fold compared to human steady-steady AUCng*hr/mL of BHS697 on Day 15 at clinical dose 125 QD. Considering the lack of safety margins in pivotal toxicity studies in dogs, the applicant is asked to discuss the overall clinical relevance of safety findings in this toxicological species.

The safety margins at all dose levels in all studies was <1 based on a comparison of Cmax or AUC values in rat and dog toxicity studies to the human exposure (5364 ng*hr/mL; Cycle 1, Day 15) at the recommended dose of 125 mg QD, reflecting the greater sensitivity of the species used in the nonclinical toxicology programme to the pharmacologic effects (ie, inhibition of FGFR1-3) of infigratinib.

The following text is proposed to be added in section 5.3 of the SmPC:

The highest plasma exposures achieved in the repeat-dose toxicology studies were associated with significant toxicity, including mortality, and were below the tolerated plasma exposures in patients at the highest recommended dose of 125 mg QD, suggesting humans are less sensitive than preclinical species to the toxicities of infigratinib. Clinically relevant exposures were not attained in the species used in the toxicology studies, therefore these studies have a limited value in producing clinically relevant safety data on infigratinib.

Genotoxicity studies submitted are considered sufficient for characterisation of the genotoxic potential of Infigratinib and its main metabolites. All information concerning genotoxicity is indicated in the relevant section 5.3 of the SPC except the lack of a safety margin in the *in vivo* micronucleus test that should be mentioned in section 5.3 of the SPC.

The proposed indication of Febseltiq falls into the scope of the ICH S9 guideline, and thus studies on potential effects of infigratinib on reproduction and development can be reduced to embryo-foetal developmental evaluation. Nevertheless, a complete programme of reproductive and developmental toxicity studies has been performed with infigratinib, including studies on fertility and early embryonic development in rats, dose-range-findings and definitive embryo-foetal developmental studies in rats and rabbits and a pre- and postnatal developmental study in rats. Exposures of infigratinib and its major human metabolites were only reached in the animals which were only far below the human exposure at the recommended human dose (RHD). This limits the relevance of the studies for humans in particular with regard to no observed effects in the studies.

Although, no effects on male and female fertility were observed in rats, literature data suggest a role of FGFs and FGFRs in spermatogenesis and folliculogenesis and thus a potential for impacting fertility. Since

the estimated exposure in the study at 3 mg/kg/day is expected to be only far below the human exposure at the RHD, the study has some limitations for investigating the impact on fertility in relation to the clinical exposure. Therefore, the findings from the literature should also be considered for risk assessment and risk communication. This should be addressed in the SmPC wording.

Infigratinib-related embryo-foetal toxicity and - lethality were observed in all reproductive and developmental toxicity studies in rats and/or rabbits. Based on the mechanism of action of infigratinib (inhibitor of FGFR1-3), the effects on embryo-foetal development seen in the reproductive and developmental toxicity studies should be regarded as relevant for humans and infigratinib should be classified as a suspected human teratogen. This has been adequately addressed in section 4.6 of the SmPC. However, in section 5.3 of the SmPC only the results from the fertility and early embryonic study are mentioned. The main clinically relevant findings from the other reproductive and developmental studies with infigratinib should also be added.

A time period of 1 month after end of treatment with infigratinib for use of effective contraception in male and females and for the discontinuation of breast-feeding is proposed in the product information. A justification has not been provided by the applicant.

Juvenile toxicity studies are not required based on the current patient population and no studies have been submitted by the applicant. However, a juvenile toxicity study with infigratinib is mentioned (Study No. 20163480) in the study reports of the DRF-EFD studies in rats and rabbits which provides the basis for the dose levels used in these studies. This study should be submitted.

3.2.7. Conclusion on non-clinical aspects

In vitro activity of infigratinib was not evaluated in cholangiocarcinoma cell lines. In one patient-derived xenograft, partial response was observed only some animals. In another cholangiocarcinoma model, tumour growth inhibition was reversible after the last dose. Therefore, the demonstration of the non-clinical proof-of-principle for the proposed indication is a major concern. The accumulation of infigratinib in liver and BHS697 in liver, kidneys and brain is an issue to be clarified. In addition, missing data should be submitted and methodological issues need to be resolved. From a toxicology point of view, there are several other concerns raised. These apply to the safety margins below 1 as well as missing data and unclear notations in original study reports.

Conclusion on infigratinib authorisation can only be drawn provided that the concerns are adequately addressed.

3.3. Clinical aspects

Infigratinib (formerly BGJ398, also known as BBP-831 and infigratinib phosphate) is an orally bioavailable, potent, selective ATP-competitive inhibitor (tyrosine kinase inhibitor) of the FGFRs 1, 2, and 3, which has demonstrated antitumour activity in nonclinical *in vitro* and *in vivo* tumour models harbouring FGFR genetic alterations.

- **Tabular overview of clinical studies**

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
5.3.1 Reports of biopharmaceutic studies								
5.3.1.1 Bioavailability (BA) Study reports and related information (Not applicable)								
5.3.1.2 Comparative BA and bioequivalence (BE) Study reports and related information								
PK, BA	CBGJ398A 2104 1 USA	Evaluate the BA, safety and tolerability of 2 formulations of infigratinib (FMI II and CSF capsules) and the PK of metabolites BHS697 and CQM157 AUC_{last}, AUC_{inf}, C_{max}, T_{max}	Phase 1, R, OL, XO Uncontrolled Completed (30 subjects) 31JUL2014	Infigratinib single PO doses under fasting conditions; 14-day washout between doses. Formulations FMI II and CSF; 125 mg. Treatment Sequence 1 – FMI II, then CSF Treatment Sequence 2 – CSF, then FMI II	30 enrolled and treated 23M/7F 35.4 (21-54) years	Healthy, 18-55 years of age	2 single doses	Complete; CSR
PK, BA	CBGJ398X 2103 1 USA	Assess the effect of food on PK of single doses of FMI I, the relative BA of CSF and FMI I formulations under fasted conditions, and assess safety and food effect on PK and BA of metabolites BHS697 and CQM157 AUC_{last}, AUC_{inf}, C_{max}, T_{max}	Phase 1, R, OL, XO, 4-treatment, 4-sequence, 4-period, fed and fasted Uncontrolled Completed (24 subjects) 08MAY2014	Infigratinib single PO doses; 14-day washout between doses. Formulations FMI I and CSF; 100 mg. Treatment A: CSF fasted Treatment B: FMI I fasted Treatment C: FMI I with low-fat, low-calorie meal Treatment D: FMI I with high-fat, high-calorie meal	24 enrolled and treated 21M/3F 33.6 (22-55) years	Healthy, 18-55 years of age	4 single doses	Complete; CSR

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
BA, PK	CBGJ398X 2105 1 USA	Evaluate the BA and safety of 2 formulations of infigratinib (FMI II and CSF capsules) and determine PK of metabolites BHS697 and CQM157 AUC_{last}, AUC_{inf}, C_{max}, T_{max}	Phase 1, R, OL, XO, 4-treatment, 4-sequence, fed and fasted Uncontrolled Completed (40 subjects) 16JUL2015	Infigratinib single PO doses; 14-day washout between doses. Formulations FMI II and CSF. Treatment A: 125 mg CSF fasted Treatment B: 75 mg FMI II with low-fat, low-calorie meal Treatment C: 125 mg FMI II with low-fat, low-calorie meal Treatment D: 200 mg FMI II fasted	40 enrolled and treated 32M/8F 37.2 (22-54) years	Healthy, 18-55 years of age	4 single doses	Complete; CSR
PK, BA	CBGJ398X 2106 1 USA	Evaluate the BA, PK food effect, and safety of 2 formulations of infigratinib (FMI III and CSF capsules) AUC_{last}, AUC_{inf}, C_{max}, T_{max}	Phase 1, R, OL, XO, 4-treatment, 4-sequence, 4-period, fed and fasted Uncontrolled Completed (40 subjects) 13JAN2016	Infigratinib single PO doses; 14-day washout between doses. Formulations FMI III and CSF. Treatment A: 125 mg CSF fasted Treatment B: 75 mg FMI III fasted Treatment C: 125 mg FMI III fasted Treatment D: 125 mg FMI III with high-fat, high-calorie meal	40 enrolled and treated 32M/8F 36.8 (23-51) years	Healthy, 18-55 years of age	4 single doses	Complete; CSR
5.3.1.3 In Vitro - in Vivo correlation Study reports and related information (Not Applicable)								
5.3.2 Reports of studies pertinent to pharmacokinetics using human biomaterials								
5.3.2.1 Plasma protein binding study reports and related information								

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
	DCN 4008875 NA NA	Determine infigratinib, CQM157, BHS697, and BQR917 in human K_2-EDTA plasma/rapid equilibrium dialysis free fraction of human K_2-EDTA plasma (1:9) by LC-MS-MS MS (No endpoint specified)	Analysis of study samples NA NA	Infigratinib and metabolites in human plasma	NA	NA	NA	Complete; method validation report
5.3.2.2 Reports of hepatic metabolism and drug interaction studies								
PK (extrinsic)	QBGJ398-102 1 USA	Determine effect of rifampin on PK of infigratinib and the safety and tolerability of infigratinib when administered with rifampin AUC_{0-t}, AUC_{0-inf}, AUC_{Extrap}, T_{max}, T_{last}, C_{last}, and C_{max}	Phase 1, OL, fixed-sequence, 2-treatment, drug-drug interaction Uncontrolled Completed (20 subjects) 05DEC2018	Infigratinib single doses. Period 1: 125 mg infigratinib PO fasted on Day 1 Infigratinib washout: 13 days (Days 1-13) Period 2: 600 mg rifampin PO QD on Days 5-13; 125 mg infigratinib PO + 600 mg rifampin PO fasted on Day 14	20 enrolled and treated 17M/3F 37.3 (20-53) years	Healthy, 18-55 years of age	2 single doses (Day 1 and Day 14)	Complete; CSR
PK (extrinsic)	QBGJ398-103 1 USA	Determine effect of itraconazole on PK of infigratinib and the safety and tolerability of infigratinib when administered with itraconazole AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{1/2}$, CL/F, V_2/F	Phase 1, OL, fixed-sequence, 2-period, 2-treatment, drug-drug interaction Uncontrolled Completed (20 subjects) 04DEC2018	Infigratinib single doses. Period 1: 75 mg infigratinib PO fasted on Day 1 Infigratinib washout: 14 days (Days 1-14) Period 2: 200 mg itraconazole PO QD on Days 12-14; 75 mg infigratinib PO + 200 mg itraconazole PO fasted, Day 15	20 enrolled and treated 10M/10F 40.5 (19-55) years	Healthy, 18-55 years of age	2 single doses (Day 1 and Day 15)	Complete; CSR

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK (extrinsic)	QBGJ398-104 1 USA	Determine effect of lansoprazole on PK of infigratinib and the safety and tolerability of infigratinib when administered with lansoprazole AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{1/2}$, CL/F, V_2/F	Phase 1, OL, fixed-sequence, 2-period, 2-treatment, drug-drug interaction Uncontrolled Completed (20 subjects) 03DEC2018	Infigratinib single doses. Period 1: 125 mg infigratinib PO fasted on Day 1 Infigratinib washout: 14 days (Days 1-14) Period 2: 30 mg lansoprazole PO QD on Days 11-14; 125 mg infigratinib PO + 30 mg lansoprazole PO fasted on Day 15; 30 mg lansoprazole PO QD on Days 16 and 17	20 enrolled and treated 15M/5F 41.0 (23-55) years	Healthy, 18-55 years of age	2 single doses (Day 1 and Day 15)	Complete; CSR
PK (extrinsic)	QBGJ398-106 1 USA	Determine effects of multiple, QD oral doses of infigratinib on the PK of single oral doses of midazolam and the safety and tolerability of infigratinib when administered with midazolam AUC_{0-t}, AUC_{0-inf}, C_{max}	Phase 1, single-dose, OL, fixed-sequence, 2-period, 2-treatment, drug-drug interaction Uncontrolled Completed (20 subjects) 18FEB2019	Infigratinib multiple doses. Period 1: single dose 2 mg midazolam PO fasted on Day 1 Infigratinib washout: 3 days (Days 1-3) Period 2: 125 mg infigratinib PO fasted overnight for 6 days (Days 4-9); single dose of 125 mg infigratinib + 2 mg midazolam PO fasted on Day 10	20 enrolled and treated 18M/2F 34.1 (19-45) years	Healthy, 18-55 years of age	7 days (Day 1 and Days 4-10)	Complete; CSR

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK (extrinsic)	QBGJ398-111 2 USA	Determine effects of multiple, BID oral doses of famotidine on the PK of a single oral dose of infigratinib and the safety and tolerability of infigratinib when administered with famotidine C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, CL/F, V_z/F	Phase 1, single-dose, OL fixed sequence, 3-period, 3-treatment, drug-drug interaction Uncontrolled Completed (20 subjects planned) 29SEP2020	Period 1: infigratinib 4 mg, single dose PO fasted on Day 1 Infigratinib washout: 14 days (Days 1-14) Period 2: infigratinib 125 mg single dose PO fasted on Day 15 Infigratinib washout: 14 days (Days 15-28) Period 3: famotidine 40 mg BID PO (Days 25-29). Infigratinib 125 mg single dose fasted on Day 29 (after the morning dose of famotidine)	21 enrolled (18 completed) 16M/5F 36.0 (25-50)	Healthy, 18-55 years of age	3 days (Day 1, 15, and 29)	Complete, CSR
5.3.2.3 Reports of studies using other human biomaterials (Not Applicable)								
5.3.3 Reports of human pharmacokinetic (PK) studies								
5.3.3.1 Healthy subject PK and initial tolerability Study reports and related information								
PK	4007675 1 USA	Profiling and characterisation of infigratinib metabolites in human plasma, urine, and feces, in support of QBGJ398-101	NA	Infigratinib and metabolites in human plasma, urine, and feces	NA	NA	NA	Complete, metabolite report

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK	QBGJ398-101 1 USA	Determine mass balance, routes and rates of elimination of total radioactivity, and PK of infigratinib and metabolites (CQM157, BHS697, and BQR917), the chemical structure of the metabolites, and the safety and tolerability of infigratinib C_{max}, T_{max}, C_{last}, T_{last}, λ_z, $T_{1/2}$, AUC_{last}, AUC_{inf}, total radioactivity in urine and feces	Phase 1, OL, single-radiolabeled dose, not randomised Uncontrolled Completed (8 subjects) 10DEC2018	Infigratinib single PO dose 125 mg (as free base) containing 150 µCi of [^{14}C] infigratinib (fasted)	8 enrolled and treated 8M/0F 34.4 (26-50) years	Healthy males, 18-55 years of age	Single dose	Complete; CSR
PK	QBGJ398-109 1 USA	Evaluate PK, safety and tolerability of infigratinib FMI IV formulation AUC_{0-24}, AUC_{inf}, and C_{max}, AUC_{last}, $\%AUC_{extrap}$, T_{max}, $T_{1/2}$, CL/F and V_z/F	Phase 1, OL, 1-period, PK Uncontrolled Completed (20 subjects) 12JUL2019	Infigratinib single PO dose 125 mg (fasted) FMI IV formulation	20 enrolled and treated 17M/3F 36.8 (19-53) years	Healthy, 18-55 years of age	Single dose	Complete, CSR

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK	QED-001 Refer to CBGJ398X2103 CBGJ398A2104 CBGJ398X2105 CBGJ398X2106 QBGJ398-109	Compare CSF, FMI I, FMI III, and FMI IV formulations (No endpoint specified)	NA	Infigratinib	NA	NA	NA	Complete; PK report
5.3.3.2 Patient PK and initial tolerability Study reports and related information								
PK, PD	CBGJ398X2102 22 USA, Spain, France, Italy, Australia, Belgium, Canada, Germany, Netherlands, Republic of Korea, Singapore, Switzerland	Determine MTD and/or RDE, safety and tolerability, PK, and preliminary antitumour activity Estimation of probability of DLT in Cycle 1	Phase 1b, multicentre, OL, dose escalation and expansion, PK Uncontrolled Completed (50 subjects) 02OCT2013	Infigratinib PO QD (3 weeks on/1 week off) + alpelisib QD (28-day cycles) Dose groups infigratinib + alpelisib (1) 20 mg + 300 mg (2) 20 mg + 400 mg (3) 40 mg + 300 mg (4) 75 mg + 300 mg (5) 90 mg + 300 mg (6) 100 mg + 300 mg (7) 125 mg + 300 mg	62 enrolled and treated 23M/39F 58.4 (30-78) years	Escalation: Advanced solid cancers with PIK3CA mutations Expansion: Advanced solid cancers (except CRC) with PIK3CA mutations with or without FGFR mutations, amplifications, or translocations	28-day cycles until disease progression, study termination, or other DC reason	Complete; CSR

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK, PD	CBGJ398X1101 8 Japan China	Estimate MTD and/or RDE, safety and tolerability, PK, and preliminary antitumour activity Incidence rate and category of DLTs in Cycle 1	Phase 1, multicentre, OL, dose finding, dose-escalation and expansion Uncontrolled Complete (35-38 subjects 19OCT2012	Escalation: Infigratinib PO, QD or BID: 50, 100, 125, 150, 175, 200 mg Safety run in (Chinese only): ≤MTD/RDE for Japanese Expansion (not done; study terminated): Infigratinib TBD (QD or BID) PO	9 enrolled and treated (Escalation: 6 Japanese subjects; Safety run in: 3 Chinese subjects) 8M/1F 56.4 (25-66) years	Escalation: Japanese subjects with advanced solid tumours with FGFR1 or FGFR2 amplification, FGFR3 mutation or other FGFR alteration for which no further standard therapy existed Safety run-in: Chinese subjects, same diagnosis as for Escalation	28-day cycles until disease progression, study termination, or other DC reason	Complete; CSR
PK, PD	CBGJ398X2101 38 Austria, France, Germany, Israel, Italy, Republic of Korea, Netherlands, Singapore, Spain, Thailand, USA	Determine MTD, RPTD, and schedule of infigratinib administration; preliminary antitumour activity in Arm 4; safety and tolerability at the RPTD; PK; determine optimal biological dose; evaluate potential predictive biomarkers Incidence rates and categories of DLTs	Phase 1, multicentre, OL, dose-finding Uncontrolled Completed (153 subjects) 09NOV2009	Infigratinib PO: 28-day dosing cycles Formulations: FMI I and CSF Escalation: Continuous QD: 5, 10, 20, 40, 60, 100, 125, 150 mg; BID: 50 mg Expansion: *Arms 1 and 2*: 125 mg, continuous QD *Arms 3 and 4*: 125 mg, 3 weeks on 1 week off	208 enrolled and treated 112M/96F 60.4 (25-86) years	Histologically/ cytologically confirmed advanced solid tumours carrying any FGFR mutation, amplification or gene fusion, for whom no effective standard therapy exists	28-day cycles until disease progression, study termination, or other DC reason	Complete; CSR

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK	QEDT-NCA-BGJ398-827 Refer to CBGJ398X2204 (Interim CSR)	Characterise the PK profile of infigratinib 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 (No endpoint specified)	NA	Infigratinib	NA	NA	NA	Complete; PK report
PK	QEDT-NCA-BGJ398-827 v4 Refer to CBGJ398X2204 (Primary CSR)	Characterise the PK profile of infigratinib 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 (No endpoint specified)	NA	Infigratinib	NA	NA	NA	Complete; PK report
5.3.3.3 Intrinsic factor PK Study reports and related information								
PK (intrinsic)	QBGJ398-107 1 USA	Assess PK, safety, and tolerability of infigratinib in subjects with chronic hepatic impairment and matched healthy adults C_{max}, T_{max}, C_{last}, T_{last}, λ_z, $T_{1/2}$, AUC_{0-t}, AUC_{inf}, AUC_{Extrap}, CL/F, V_z/F	Phase 1, NR, OL, parallel-group Uncontrolled Completed (40 subjects) 27FEB2019	Infigratinib 125 mg PO, single dose, fasted	40 planned and treated 24M/16F 58.7 (35-79) years	Chronic hepatic impairment (Child-Pugh Class A or B); Matching healthy	Single dose	Complete, CSR

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK (intrinsic)	QBGJ398-110 4 USA	Assess PK, safety, and tolerability of infigratinib in subjects with renal impairment and matched healthy adults C_{max}, T_{max}, C_{last}, T_{last}, λ_z, $T_{1/2}$, AUC_{0-24}, AUC_{last}, AUC_{inf}, AUC_{Extrap}, CL/F, CL_{NR}/F, V_z/F	Phase 1, NR, OL, parallel-group Uncontrolled Completed (40 subjects planned) 09OCT2019	Infigratinib 125 mg PO, single dose, fasted	14 enrolled and treated 8M/6F 63.0 (50-75) years	Moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2); Matching healthy (eGFR ≥90 mL/min/1.73 m^2)	Single dose	Complete, CSR
5.3.3.4 Extrinsic factor Study reports and related information (Not Applicable)								
5.3.3.5 Population PK Study reports and related information								

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK	QED-PMX-001 Refer to CBGJ398X2103 CBGJ398A2104 CBGJ398X2105 CBGJ398X2106 QBGJ398-102 QBGJ398-103 QBGJ398-104 QBGJ398-109 CBGJ398X1101 CBGJ398X2101 CBGJ398X2102 CBGJ398X2201 CBGJ398X2204 (March 2020 cutoff)	Develop population PK models for infigratinib, BHS697, and CQM157 using pooled plasma drug concentration data from selected Phase 1 and Phase 2 studies, and evaluate impact of intrinsic and extrinsic factors on PK variability of infigratinib, BHS697, and CQM157; examine formulation effects on infigratinib PK; examine covariates (eg, age, body weight, sex, etc) to identify predictors of PK variability in infigratinib, BHS697, and CQM157; and predict individual infigratinib, BHS697, and CQM157 exposure measures for use in E-R analyses (No endpoint specified)	NA	Infigratinib	NA	NA	NA	Complete; Population PK report

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK	QED-PMX-004 Refer to studies listed for QED-PMX-001 and CBGJ398-107 CBGJ398-110 CBGJ398-111 CBGJ398X2204 (March 2021 cutoff)	Refine and update the previously developed population PK models for infigratinib, BHS697, and CQM157 using pooled plasma drug concentration data from selected Phase 1 and Phase 2 studies (see QED-PMX-001) (No endpoint specified)	NA	Infigratinib	NA	NA	NA	Complete; Population PK report
5.3.4 Reports of human pharmacodynamic (PD) studies								
5.3.4.1 Healthy subject PD and PK/PD Study reports and related information (Not Applicable)								
5.3.4.2 Patient PD and PK/PD Study reports and related information								

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PD,PK	QED-PKPD-001 Refer to CBGJ398X2101 CBGJ398X2204	Assess relationship between exposure of infigratinib and its major metabolites and QT/QTc to exclude clinically relevant effects on QT by infigratinib or metabolites Model-predicted change from baseline in QTc using the Fridericia correction (QTcF) method	NA	Infigratinib	NA	NA	NA	Complete; ECG report
PD, PK	QED-PMX-002 Refer to CBGJ398X1101 CBGJ398X2101 CBGJ398X2201 CBGJ398X2204 (March 2020 datacut)	Develop E-R models describing: (1) probability of OR as a function of infigratinib exposure; (2) PFS as a function of infigratinib exposure; (3) time to first occurrence of TE hyperphosphataemia; (4) time to first occurrence of TE eye disorders (excluding CSR/RPED); (5) time to first occurrence of TE CSR/RPED (No endpoint specified)	NA	Infigratinib	NA	NA	NA	Complete; E-R modeling report

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PD, PK	QED-PMX-005 Refer to CBGJ398X1101 CBGJ398X2101 CBGJ398X2201 CBGJ398X2204 (March 2021 datacut)	Update the previously developed key E-R efficacy and safety models described in QED-PMX-002. (No endpoint specified)	NA	Infigratinib	NA	NA	NA	Complete; E-R modeling report
PD, PK	QED-PMX-003 Refer to: QED-PMX-001, QED-PMX-002, QBGJ398-107 QBGJ398-110	Updated Population PK model (QED-PMX-001) to include results from QBGJ398-110 (renal impairment study) and QBGJ398-107 (hepatic impairment study) Develop PK/PD models to describe infigratinib-longitudinal changes in serum phosphate concentration and infigratinib-longitudinal changes in tumour size relationships (no endpoint specified)	NA	Infigratinib	NA	NA	NA	Complete; PK/PD modeling report
5.3.5 Reports of efficacy and safety studies								
5.3.5.1 Study reports and related information of controlled clinical studies pertinent to the claimed indication (Not Applicable)								
5.3.5.2 Study reports and related information of uncontrolled clinical studies								

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
Efficacy	CBGJ398X US04 41 USA	Assess clinical benefit (CR, PR, SD, OR, PFS, OS, DOR), safety and tolerability Clinical benefit rate (CR, PR, or stable disease ≥16 weeks for solid tumours)	Phase 2, OL, signal-seeking Uncontrolled Completed (70-90 subjects planned) 21JUL2014	Infigratinib 125 mg PO QD: 3 weeks on / 1 week off (28-day cycles)	85 enrolled 84 treated 37M/47F 60.2 (33-85) years	Solid tumour or hematologic malignancy or with a history/ evidence of TIO and FGF23-mediated hypophosphataemia with or without identification of an FGFR genetic alteration	28-day cycles until disease progression, study termination, or other DC reason	Complete; CSR
PK, Efficacy	CBGJ398X 2204 18 USA, Germany, Thailand, Singapore, Spain, Belgium, Taiwan	Determine efficacy (ORR, PFS, BOR, DOR, OS), safety and PK of infigratinib and PK of FMI III and FMI IV ORR by BICR	Phase 2, multicentre, single arm Uncontrolled Ongoing (160 subjects planned across all cohorts) 23JUL2014	Infigratinib 125 mg PO QD: 3 weeks on / 1 week off (28-day cycles) Formulations FMI I, FMI III, and FMI IV	108 Cohort 1 subjects with FGFR2 fusions enrolled and treated as of 31MAR2020 cutoff date 41M/67F 53.4 (23-81) years	Advanced or metastatic CCA with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy	28-day cycles until disease progression, study termination, or other DC reason	Ongoing; Interim CSR
PK, Efficacy	See above	See above	See above	See above	108 Cohort 1 subjects with FGFR2 fusions enrolled and treated as of 01MAR2021 cutoff date 41M/67F 53.4 (23-81) years	See above	See above	Ongoing; Primary CSR (pivotal)

Study Type	Study ID; # of Study Centres; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
Abbreviations: BA=bioavailability; BICR=blinded independent central review; BID=twice daily; BOR=best overall response; CCA=cholangiocarcinoma; CR=complete response; CRC=colorectal cancer; CSF=Clinical Service Form; CSR=clinical study report; CSR/RPED= central serous retinopathy/retinal pigment epithelium detachment; DC=discontinuation; DCR=disease control rate; DOR=duration of response; ECG=electrocardiogram; E-R=exposure-response; FGFR=fibroblast growth factor receptor; FMI=Final Market Image; Loc=location; MTD=maximum tolerated dose; NA=not applicable; NR=nonrandomised; OL=open-label; OR=overall response; ORR=overall response rate; OS=overall survival; PD=pharmacodynamic; PFS=progression-free survival; PK=pharmacokinetic(s); PO=oral; PR=partial response; QD=once daily; QOL=quality of life; QT=interval in an ECG test of heart function; QTc=duration of the QT interval adjusted for the subject's heart rate; QTcF=QTc using Fridericia correction; R=randomised; SD=stable disease; TE=treatment-emergent; TIO=tumour-induced osteomalacia; Tx=treatment; UCC=urothelial cell carcinoma; WT=wild type; XO=crossover. [a] Nomenclature for the investigational product has evolved over the development programme. The current convention is to refer to the Final Market Image followed by the appropriate formulation by Roman numeral (ie, FMI I, FMI II, FMI III, FMI IV). This terminology is used with the exception that the protocol title remained unchanged.								

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Infigratinib and its active metabolites CQM157, BHS697, and BQR917 were considered relevant to describe the pharmacokinetic (PK) and pharmacodynamic (PD) properties of infigratinib, and evaluated in 21 clinical studies. In addition, population PK modelling was conducted including the following studies relevant for the intended indication.

Table PK 1 Studies Used in the Population PK Analysis of Infigratinib and its Metabolites BHS697 and CQM157 in Healthy Subjects and Oncology Patients

Study	Population	Infigratinib Formulation	Phase	PK Sampling	Included in Population PK Analysis
CBGJ398X1101	Oncology Patients	CSF	1	Intense	Infigratinib, BHS697, CQM157
CBGJ398X2101	Oncology Patients	CSF, FMI I	1	Intense	Infigratinib, BHS697
CBGJ398X2102	Oncology Patients	CSF	1b	Intense	Infigratinib, BHS697, CQM157
CBGJ398X2103	Healthy Subjects	CSF, FMI I	1	Intense	Infigratinib, BHS697, CQM157
CBGJ398A2104	Healthy Subjects	CSF	1	Intense	Infigratinib, BHS697, CQM157
CBGJ398X2105	Healthy Subjects	CSF	1	Intense	Infigratinib, BHS697, CQM157
CBGJ398X2106	Healthy Subjects	CSF, FMI III	1	Intense	Infigratinib, BHS697, CQM157
QBGJ398-102	Healthy Subjects	FMI III	1	Intense	Infigratinib, BHS697, CQM157
QBGJ398-103	Healthy Subjects	FMI III	1	Intense	Infigratinib, BHS697, CQM157
QBGJ398-104	Healthy Subjects	FMI III	1	Intense	Infigratinib, BHS697, CQM157
QBGJ398-107	Healthy Subjects and hepatically impaired	FMI III	1	Intense	Infigratinib, BHS697, CQM157
QBGJ398-109	Healthy Subjects	FMI IV	1	Intense	Infigratinib, BHS697, CQM157
QBGJ398-110	Healthy Subjects and renally impaired	FMI IV	1	Intense	Infigratinib, BHS697, CQM157
QBGJ398-111	Healthy Subjects	FMI IV	1	Intense	Infigratinib, BHS697, CQM157
CBGJ398X2201	Oncology Subjects	FMI I	2	Sparse	Infigratinib, BHS697, CQM157
CBGJ398X2204	Oncology Subjects	FMI I, FMI III, FMI IV	2	Intense + Sparse	Infigratinib, BHS697, CQM157

Source: QED-PMX-004, Table 1 and Table 2.

For the clinical studies, Infigratinib and its metabolites was determined in human plasma samples by LC-MS/MS method in a range of 1 to 1 000 µg/mL or 0.20 to 200 ng/mL. Overall, the methods used are sufficiently described.

The validation was performed according to the Guideline on bioanalytical method validation, EMEA/CHMP/EWP/192217/2009. Sufficient chromatograms, as well as information about acceptance criteria for the exclusion of standard and QC and for repeating/re-assay, have been presented. Results of incurred samples reanalysed show the suitability of the method used. The higher acceptance criteria of 30% bias of BQR917 is acceptable. From the results of the validation can be concluded that the methods used have adequate precision, accuracy and specificity to determine Infigratinib at the concentration levels expected in real samples for all studies.

The performance of the analytical methods were successfully demonstrated during in-study method performances.

Standard methods for non-compartmental PK analyses and statistics were utilised.

Modelling

PK of Infigratinib was described using 2-compartmental models with nonstationary (infigratinib and BHS697) or stationary (CQM157) linear elimination, first-order absorption/formation rate constant and absorption/formation lag time. Infigratinib, BHS697 and CQM157 were modelled separately.

The final PK parameter estimates were consistent with the previously reported popPK models. As in previously reported popPK models, a high amount of excluded postdose BLQ samples hampers the analysis of the PK characteristics of Infigratinib (25.3%), BHS657 (30.8%) and CQM157 (18.7%). However, this could be accepted given that before calculating the percentiles of the observed concentrations in the VPCs, all BLQ observations were added back to the dataset.

High inter- and intra-individual variability in the PK of infigratinib and its major circulating active metabolites could not be fully explained by the use of covariates and hampers the interpretation of the results regarding significance. The observed decrease of CL with the number of doses might be problematic with regards to accumulation – given the fact that patients achieve higher exposures compared to healthy volunteers. Until concerns regarding modelling are not addressed the dose recommendations for patients with renal and hepatic impairment should not be given based on modelling.

The calculated AUCs for infigratinib and its two analysed metabolites were combined and weighted based on relative *in vitro* receptor activity data (binding affinity KD) to facilitate exposure response modelling. In principle, this approach is accepted, even though this method added more assumptions to the modelling process.

The goodness-of-fit plots show that the final models described the observed data for patients reasonably well, considering the high inter- and intraindividual variability. For infigratinib underprediction of HV data was observed. It should be clarified whether this underprediction might be the reason for the smaller predicted AUC compared to NCA results and if the alternatively tested Weibull model for absorption could lead to better results. Modelling output should be provided. To to be able to assess accumulation risk during multiple dosing, additional VPCs are requested showing Patients' Multiple Dose on a time scale of 24h due to the lack of multiple dose data in HV.

E-R modelling for efficacy was used to investigate the probability of confirmed OR using logistic regression. Exposure was no significant predictor of OR, so planned simulations regarding appropriateness of the clinical dose were not conducted. The analysis was limited due to small sample size (n=65). Significant E-R relationships were identified for hyperphosphataemia and eye disorders using time to first occurrence of adverse events. Higher infigratinib exposure resulted in higher probability of hyperphosphataemia and eye disorders (excluding CSR/RPED). Overall, the VPCs illustrate good agreement of the model predictions with the observed data for the exposure-response modelling regarding time to first occurrence of hyperphosphataemia and eye disorders.

Absorption

The absolute bioavailability of infigratinib has not been evaluated in humans.

In vitro, infigratinib permeability and interaction with efflux transporters was studied in Caco-2 monolayers and classified this compound as a moderately permeable compound. Infigratinib was a substrate for BCRP and P-gp efflux transporters *in vitro*.

Bioequivalence

The clinical development programme for infigratinib included five different capsule formulations of infigratinib (CSF, FMI I, FMI II, FMI III, and FMI IV). FMI IV is the formulation intended to be marketed. Relative bioavailability studies for CSF vs FMI I and CSF vs. FMI III were conducted in fasted state and showed comparable exposure of infigratinib. Relative bioavailability was also studied for CSF vs FMI II; but as FMI II produced lower infigratinib exposure this formulation was discontinued and not used in any patient studies.

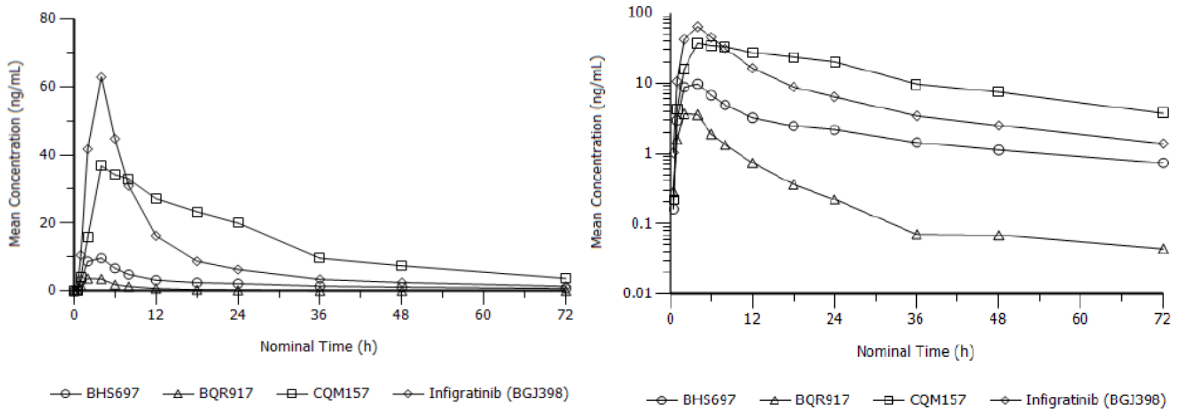
For the FMI IV formulation the open-label, one-period, single-arm, single-dose Phase 1 study QBGJ398-109 evaluated the PK of infigratinib and its metabolites after 125 mg (5×25 mg capsules) in fasted state.

Table PK 1 PK Parameters of Infigratinib and Metabolites after single-dose FMI IV in HV

		Mean (%CV)						
PK Parameter	**N**	**Infigratinib**	**N**	**CQM157**	**N**	**BQR917**	**N**	**BHS697**
T_{max} (h)[a]	20	4.00 (1.99-6.00)	20	4.07 (3.99-24.0)	20	2.03 (1.99-4.09)	20	4.00 (1.99-4.09)
C_{max} (ng/mL)	20	68.4 (75.0)	20	39.0 (56.4)	20	4.10 (51.8)	20	10.0 (57.5)
AUC_{0-24hr} (ng*hr/mL)	20	532 (97.0)	20	603 (66.0)	19 [b]	29.6 (47.4)	20	100 (58.6)
AUC_{inf} (ng*hr/mL)	17[b]	548 (82.3)	17	1170 (76.8)	18 [b]	29.6 (46.6)	16	196 (49.2)
$T_{1/2}$ (h)	18 [b]	12.0 (71.9)	17	18.5 (23.9)	19 [b]	7.06 (115)	16	26.9 (15.6)
CL/F (L/h)	17 [b]	321 (46.3)	NC	NC	NC	NC	NC	NC
Vz/F (L)	17 [b]	5330 (101)	NC	NC	NC	NC	NC	NC

[a] Reported as median (range).
[b] Data reported for number of subjects where sufficient data was available and parameters could be accurately estimated (for AUC and $T_{1/2}$ and related parameters: Rsq adjusted >0.85 and AUC_{extrap} <20%).
Source: QBGJ398-109 CSR, Table 6

Figure PK 1 Concentration-time curves of Infigratinib and Metabolites after single-dose FMI IV in HV



Source: CSR, Figure 1

A comparison of dose-normalised PK parameters pooled from five single-dose HV studies [NB: the 4 BE studies and study 109; PK report QED-001] in fasted state confirmed that the exposure between formulations was comparable.

Food effect

The food effect on infigratinib PK for formulations FMI I and FMI III was assessed in Studies X2103 and X2106, respectively (and X2105 for FMI II). Across formulations, the presence of food increased infigratinib exposure with a higher increase in AUCinf with a high-calorie, high-fat meal.

In study X2106, with high-fat, high-calorie food AUClast, AUCinf, and Cmax for FMI III 125 mg showed 2.7-, 2.2, 1.8-fold higher infigratinib exposure vs. CSF, respectively. Exposures of CQM157 and BHS were also higher.

When compared to FMI III in fasted state, fed state also resulted in exposure increases of 2.0-, 1.8-, and 1.6-fold for AUClast, AUCinf and Cmax, respectively. Exposures of CQM157 and BHS were also higher.

Table PK 2 Food-effect of FMI III vs. CSF of Infigratinib and Metabolites after single-dose

	Mean (%CV)				
	n	**Test** 125 mg FMI III, high-fat, high-calorie	n	**Reference** 125 mg CSF fasted	**%GLSM Ratio (90%CI)** (Test/Reference)
Infigratinib PK Parameter					
AUC_{last} (h*ng/mL)	33	1210 (107.1)	36	666 (180.7)	2.65 (2.13, 3.29)
AUC_{inf} (h*ng/mL) [a]	30	1330 (101.2)	33	742 (170.4)	2.20 (1.83, 2.64)
C_{max} (ng/mL)	33	78.2 (58.7)	36	53.1 (76.7)	1.81 (1.44, 2.29)
CQM157 PK Parameter					
AUC_{last} (h*ng/mL)	33	1720 (74.0)	36	1150 (80.1)	NC
AUC_{inf} (h*ng/mL) [a]	31	1880 (67.5)	33	1280 (71.8)	NC
C_{max} (ng/mL)	33	54.1 (61.2)	36	38.4 (69.1)	NC
BHS697 PK Parameter					
AUC_{last} (h*ng/mL)	32	169 (81.8)	33	136 (117.1)	NC
AUC_{inf} (h*ng/mL) [a]	11	363 (44.6)	5	447 (64.2)	NC
C_{max} (ng/mL)	32	7.03 (53.4)	33	8.23 (56.6)	NC

[a] For subjects with AUC_{extrap} >20% or Rsq adjusted<0.85, AUC_{inf} was not included in the statistical analysis.
Source: CBGJ398X2106 CSR Table 14.2-1.1.1, Table 14.2-2.1.1, Table 14.2-2.1.2, Table 14.2-2.1.3

Distribution

Protein binding to human proteins of infigratinib and its metabolites was high (>96%) *in vitro*. Consistent with *in vitro* data, infigratinib and metabolite protein binding was high (>99%) in plasma from healthy subjects on ex vivo results in the hepatic-impairment study 107.

In the mass balance study the blood-to-plasma ratio of radioactivity was approximately 0.88 until 168 hours postdose based on AUCinf, indicating distribution of infigratinib into the cellular components of blood.

In healthy volunteers after a single dose of 125mg FMI IV, geo-mean Vz/F was 3710 L (105%CV) in study 109, and was 6830 L (89.5% CV) in study 111.

In CCA patients in study X2204 with 125mg FMI IV geo-mean Vz/F on C1D1 was 1695 L (242%) and in steady-state on C1D15 3193 L (NC).

The popPK derived steady-state mean apparent volume of distribution was 1350 L (54.6 %CV) at 125 mg for a 75.4 kg subject.

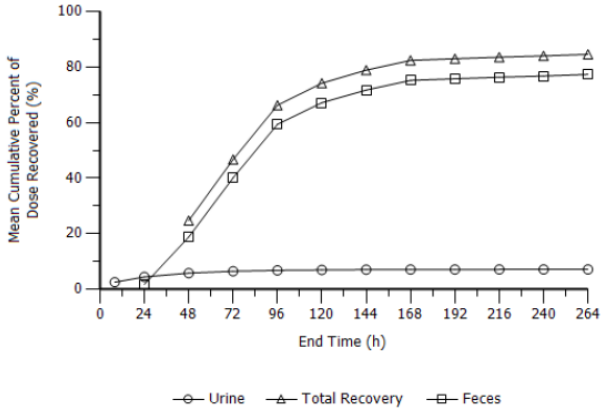
Volume of distribution of the active metabolites was not assessed.

Elimination

To evaluate excretion, mass balance, PK and metabolism 8 healthy males received a single 125 mg dose of infigratinib (as free base) oral solution containing approximately 150 µCi of [^{14}C]infigratinib after an overnight fast of ≥10 hours.

Approximately 84.5% of the radioactive dose was recovered over 264 hours, with 77.3% in faeces and 7.22% in urine.

Figure PK 2 Mean Cumulative Amount Recovered in Urine, Faeces, and Total Recovery (Percentage of Dose) after Administration of 150 µCi [^{14}C] Infigratinib



Source: QBGJ398-101 CSR, Figure 14.1.1

Table PK 3 Plasma PK Parameters of non-Radioactive Infigratinib and metabolites after SD 125 mg infigratinib free base as oral solution

	Mean (%CV)							
PK Parameter	**N**	**Infigratinib**	**N**	**CQM157**	**N**	**BQR917**	**N**	**BHS697**
T_{max} (h)[a]	8	3.50 (2.00-6.00)	8	5.05 (4.00-8.00)	8	2.50 (1.50-4.00)	8	3.00 (2.00-4.00)
C_{max} (ng/mL)	8	138 (50.45)	8	47.7 (48.35)	8	5.07 (51.17)	8	17.6 (40.48)
AUC_{inf} (h*ng/mL)	8	1480 (69.46)	8	1180 (25.23)	8	58.6 (65.97)	8	391 (47.30)
$T_{1/2}$ (h)	8	8.94 (54.46)	8	27.8 (39.52)	8	9.53 (67.34)	8	42.7 (38.50)
CL/F (L/h)	8	142 (73.90)	-	NC	-	NC	-	NC
V_Z/F (L)	8	1360 (48.62)	-	NC	-	NC	-	NC

AUC_{inf}=area under the concentration-time curve from time 0 to infinity; C_{max}=maximum observed concentration; CV=coefficient of variation; N=number; NC=not calculated; PK=pharmacokinetic; $T_{1/2}$=half-life; T_{max}=time to maximum observed concentration; Vz/F=apparent volume of peripheral compartment.
[a]Reported as median (range).
Source: QBGJ398-101 CSR, Table 10

Excretion of unchanged infigratinib was low, 3.43% of dose in faeces and 1.90% of dose in urine, indicating extensive metabolism.

The predominant species in faeces was a mixture of BHS697/M24/M25 (21.6% of dose) and M27 (11.8%). Other minor metabolites were detected, including M35 and M36 (0.09% and 0.08% of dose). 29.5% of dose was recovered as previously unidentified metabolites (with 0.104% to 6.11% of dose).

The predominant species in urine was the mixture of BHS697/M24/M25 (2.38%), minor metabolites included M27 and BQR917 (0.54 and 1.17% of dose, respectively) and 4 unknown metabolites (0.022% to 0.07% of dose).

Infigratinib was the predominant component in plasma with AUClast of 37.9% of drug-related exposure; however, total plasma radioactivity available for chromatographic resolution was low and not all metabolites could be resolved. The second most abundant species in plasma (34.40%) was the mixture BHS697/M24/M25. Metabolites M35, M27, and Unknown 1 were found at 27.36%, 0.31%, and 0.06% of drug-related exposure, respectively.

Metabolism

Based on *in vitro* experiments, infigratinib hepatic metabolism occurred mainly via CYP3A4 (~92%) with a minor contribution by FMO3 (6%) and very minor contributions by CYP2D6 and CYP2J2. With an

anticipated total clearance contribution of <1%, the effect of CYP2D6 polymorphism on infigratinib PK variability is likely very low.

The metabolite:parent ratio at steady state in rank order was BHS697 > CQM157 > BQR917.

The mean metabolite:parent ratio for BHS697 showed no significant change in oncology patients after multiple dose relative to single dose and HV with 16-44%. BQR917 was at 5-13% in all populations.

The mean metabolite:parent ratio for CQM157 was variable across studies and populations. After multiple dosing in oncology patients, the CQM157 to parent ratio decreased to 11-15%, compared to 68-124% after single dose.

From the two major circulating metabolites (>10%), BHS697 contributes approximately 16% to 33% of FGFR1-3 inhibition. CQM157 contributes approximately 9% to 12% of FGFR1-3 inhibition.

Dose proportionality, time dependencies and variability

In vitro, infigratinib showed an inhibitory potency for CYP3A4/5 with an IC_{50} ~2 µM (~1.6 µM unbound) and a mixed (partial) inhibition mechanism with a Ki=0.26 µM (0.23 µM unbound). Very weak time-dependent inhibition of CYP3A4/5 was observed, and the inhibition was infigratinib concentration-dependent (Ki: 37.3 µM and kinact: 0.0547 min^{-1}) and confirmed to be NADPH-dependent. The observed loss of CYP3A4/5 activity could be partially attenuated by addition of GSH in the preincubation media.

BQR917 did very weakly inhibit CYP3A4/5, with a Ki of 24.7 µM and a kinact of 0.0438 min^{-1}. The observed loss of CYP3A4/5 activity could not be attenuated by addition of GSH.

In the **dose finding study X2101 in advanced solid tumour patients** infigratinib doses of FMI I were 5, 10, 20, 40, 60, 100, 150mg QD, 50mg BID, 125mg continuous and 125mg 3 weeks on/1 week off were tested in dose escalation part 1, and in part 2 patients were treated at the MTD dosing schedule (once daily or BID) or using an alternative schedule of 3 weeks on, 1 week off (28-day cycles).

Exposure to infigratinib appeared to increase more than dose proportional over the dose range 5 mg to 150 mg QD which was not significant after single-dose. However, at 5 mg and 10 mg doses a large proportion of the observations were BLQ, therefore parameters were often not calculable. Following multiple dosing, infigratinib exposures increased more than dose proportional which was significant with Cmax (1.45-fold) and AUC0-24 (1.89-fold) on Day 15.

Infigratinib accumulated significantly following repeated dosing (0.79 to 8.00-fold, with 8.00-fold at the 125 mg 3 weeks on / 1 week off regimen). On study day 28 in the respective dosing arms of study X2101 accumulation ratio was 6.4-8.6-fold between 60-125 mg.

Steady-state exposure of infigratinib was achieved on Day 15 as shown by minimal change in accumulation ratio (R_{acc}) on Day 28 compared to Day 15 following 125 mg dosing.

The median half-life of infigratinib in oncology patients on 125 mg 3 weeks on / 1 week off was 5.0 h after a single dose and 11.0 h at steady state.

Table PK 4 Study X2101: Mean Infigratinib PK Parameters Following Single- and Multiple-Dose Administration of Infigratinib (5-150 mg) in Oncology Patients

	Single Dose Infigratinib PK Parameters[a] Day 1				
Dose[b]	**AUC_{0-24hr} (ng*hr/mL)**	**C_{max} (ng/mL)**	**T_{max} (h)**	**$T_{1/2}$ (h)**	**R_{acc}**
5 mg (N=3)	**9.22** n=1	**2.17** (41.5) n=2	**2.44** [2.05; 2.83] n=2	**4.35** [4.35; 4.35] n=1	**--**
10 mg (N=3)	**1.62** n=1	**1.82** (8.5) n=2	**1.46** [1; 1.92] n=2	N/A	--
20 mg (N=4)	**71.8** (53.3) n=3	**15.8** (23.5) n=4	**2.04** [2; 3.02] n=4	**2.69** [2.62; 8.16] n=3	**--**
40 mg (N=6)	**169** (35.6) n=5	**27.2** (43.5) n=6	**2.08** [2.03; 8] n=6	**4.15** [1.91; 7.3] n=4	--
50 mg BID (N=4)[c]	**57.2** (39.0) n=3	**15.0** (5.3) n=3	**3.00** [2; 3] n=3	N/A	**--**
60 mg (N=3)	**264** (30.4) n=3	**42.4** (61.2) n=3	**2.00** [2; 6.03] n=3	**5.61** [5.18; 6.05] n=2	--
100 mg (N=6)	**467** (95.9) n=6	**72.1** (117.1) n=6	**3.02** [2.03; 3.13] n=6	**5.71** [2.51; 11.9] n=6	**--**
125 mg (N=56)	**736** (76.9) n=44	**91.2** (77.7) n=56	**3.00** [1.97; 22.5] n=56	**5.25** [2.08; 13.2] n=40	--
125 mg 3 wks on / 1 wk off (N=45)	**768** (80.7) n=41	**85.5** (62.4) n=45	**3.00** [1; 8.07] n=45	**5.00** [1.74; 13.3] n=36	**--**
150 mg (N=6)	**678** (50.7) n=6	**119** (89.1) n=6	**2.63** [1.92; 4] n=6	**5.20** [3.77; 7] n=6	--
	Multiple Dose Infigratinib Day 15				
Dose[b]	**AUC_{0-24hr} (ng*hr/mL)**	**C_{max} (ng/mL)**	**T_{max} (h)**	**$T_{1/2}$ (h)**	**R_{acc}**
5 mg (N=3)	N/A	**2.87** (20.7) n=2	**2.02** [2; 2.03] n=2	N/A	N/A
10 mg (N=3)	**4.70** n=1	**1.50** (15.1) n=2	**1.50** [1; 2] n=2	N/A	N/A
20 mg (N=4)	**213** (99.0) n=4	**20.9** (20.5) n=4	**1.99** [1.98; 3] n=4	**5.91** [2.53; 69.1] n=4	**2.82** (56.3) n=3
40 mg (N=6)	**183** (61.6) n=4	**30.2** (61.6) n=5	**2.07** [1; 4.08] n=5	**6.17** [1.94; 21] n=3	**0.789** (58.4) n=3
50 mg BID (N=4)[c]	**334** n=1	**57.0** (74.6) n=3	**4.02** [3.95; 5.97] n=3	N/A	N/A
60 mg (N=3)	**1010** (47.4) n=3	**80.4** (55.4) n=3	**2.08** [2; 6.02] n=3	**9.84** [9.25; 10.4] n=2	**4.33** (67.6) n=3
100 mg (N=6)	**1350** (92.8) n=4	**137** (76.6) n=5	**3.00** [2.02; 6] n=5	**7.03** [4.53; 13.7] n=4	**5.68** (61.5) n=4
125 mg (N=56)	**3730** (69.0) n=34	**230** (60.1) n=47	**4.00** [1; 8] n=47	**12.1** [5.05; 33.9] n=24	**7.00** (72.5) n=26
125 mg 3 wks on / 1 wk off (N=45)	**3230** (59.4) n=25	**214** (50.9) n=35	**4.12** [0; 22.7] n=35	**11.0** [5.36; 18.3] n=13	**8.00** (85.2) n=22
150 mg (N=6)	**1570** (106.8) n=4	**134** (103.9) n=4	**3.00** [1.97; 6] n=4	**9.34** [7.45; 18.1] n=3	**3.38** (86.2) n=3

[a] Data are presented as mean (%CV), except for T_{max} and $T_{1/2}$, which are presented as median [min, max].
[b] Administered 1 hour before or 2 hours after a meal.
[c] For 50 mg BID dosing AUC_{0-8h} is reported instead of AUC_{0-24hr}.
Source: CBGJ398X2101 Interim CSR, Table 11-6

In CCA patients in study X2204 accumulation of infigratinib after FMI IV for mean AUC and Cmax was ~4-5.8-fold at D15 and 7-10.8-fold for BHS697. In contrast after multiple doses, lower exposure of CQM157 on C1D15 than C1D1 was observed (0.5-0.6-fold). A decrease in infigratinib geo-mean CL/F was observed from Day 1 to Day 15 (97.4 L/h vs 22.4 L/h) for FMI III as well as for FMI IV (Day 1= 157 L/h and Day 15 = 39.6 L/h).

In CCA patients at the proposed 125 mg dose scheme, inter-subject variability (geo-mean %CV) was 92% and 72% for D15 steady-state AUC0-24hr and Cmax, respectively.

In HV with FMI IV after single dose, the inter-subject variability for infigratinib Cmax was 75 %CV and AUCinf 84 %CV. The inter-subject variability for the metabolite exposure was moderate to high with Cmax (52-58 %CV) and AUCinf (47-77 %CV).

Pharmacokinetics in the target population

In the **target CCA population** in **phase II study X2204** infigratinib 125mg was administered as FMI I, FMI III and FMI IV at the MTD of 125mg 3 weeks on/1 week off-scheme, that was the RP2D from the dose finding study.

Figure PK 3 Mean (±SD) Concentration-Time Profiles of Infigratinib, BHS697 and CQM157 after 125 mg Infigratinib (FMI III) – C1D1 (left) and C1D15 (right)

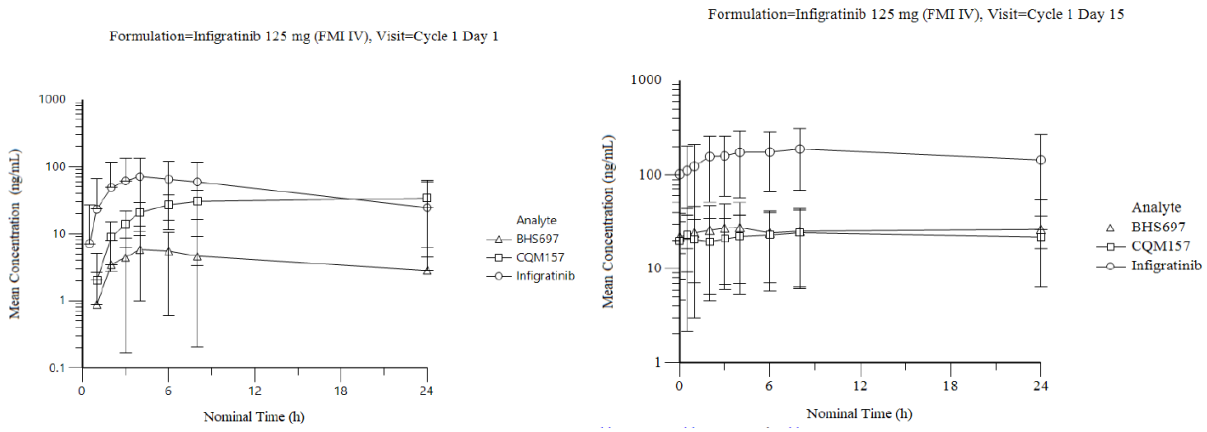
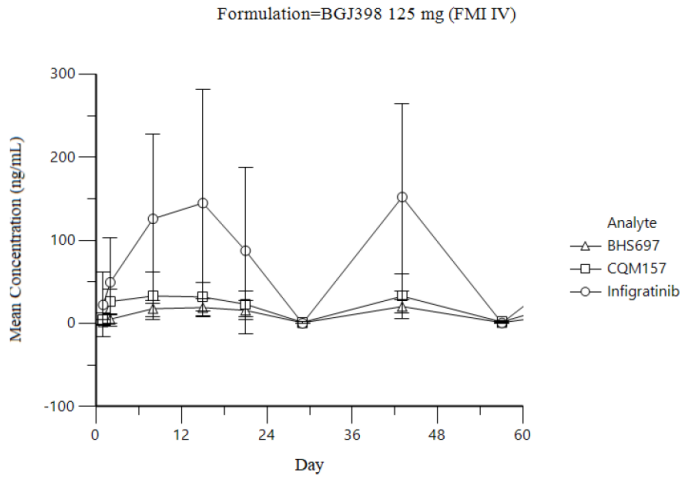


Fig 5.3.3.1 and 5.3.3.2

Figure PK 4 Mean (±SD) Trough Concentration-Time Profiles of Infigratinib, BHS697 and CQM157 after Infigratinib 125 mg – Sparse Sampling Group (FMI IV)



Source: CSR Fig 9.1.2.3

Table PK 5 Summary PK of AUC and Cmax from CCA study X2204 at C1D15

	Analyte		
	Infigratinib	BHS697	CQM157
	Infigratinib 125 mg N = 24	Infigratinib 125 mg N = 24	Infigratinib 125 mg N = 24
PK Parameter	Geo Mean (GeoMean CV%)[Arithmetic Mean, CV%]; n		
AUC_{0-24} (h*ng/mL)	4368 (92.0) [5364, 53.3]; 14	629.5 (107.1) [841.0, 70.7]; 13	353.3 (65.9) [413.1, 56.6]; 11
AUC_{last} (h*ng/mL)	4004 (88.0) [4958, 57.4]; 20	697.7 (97.3) [909.8, 68.3]; 20	373.4 (84.8) [472.1, 67.8]; 20
C_{max} (ng/mL)	248.7 (71.7) [294.7, 54.2]; 20	37.26 (95.3) [48.78, 71.1]; 20	19.03 (85.3) [23.95, 65.0]; 20

Source: Report QEDT-NCA-BGJ398-827 Version 4 Table 5.3.4.2

A major finding of the popPK model-based analysis (report PMX-004) was the decrease of infigratinib CL_{app} with the number of administered doses. CL_{app} decreased up to 79.2% with increasing numbers of doses via an estimated maximum pharmacologic effect-type relationship. The estimated number of doses for a 50% reduction of CL_{app} was 2.78; in patients with CCA, this translated to a drop in CL_{app} from 295 L/h at the first dose to 80.5 L/h after the 21st dose.

After adjusting for other covariates, including organ impairment, the estimated average CL_{app} was reduced by 32.3% in patients with glioblastoma or CCA, relative to HV.

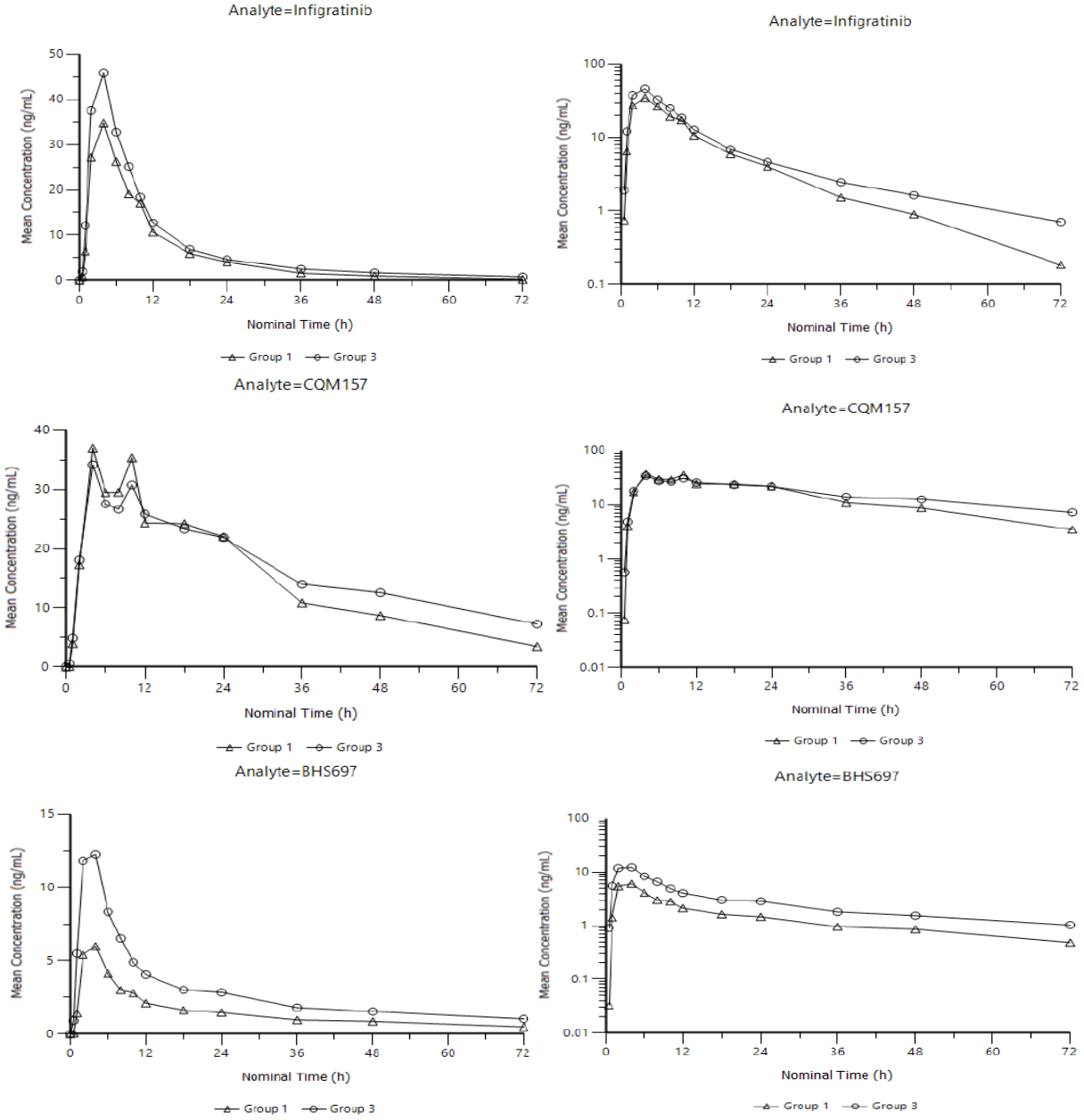
Special populations

Renal impairment

Study QBGJ398-110 evaluated the PK in plasma and urine in subjects with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2) and in matched healthy subjects (eGFR ±90 mL/min/1.73 m^2) after a single 125 mg infigratinib dose (5×25 mg capsules) after an overnight fast of ≥10 hours.

For inclusion, renal function in subjects with renal impairment was calculated based on MDRD, and in healthy subjects calculated by Cockcroft-Gault (CG) equation.

Figure PK 5 Mean Plasma Infigratinib and metabolite concentration-time curves for moderate RI (Group 3) and Matched HV (Group 1)



Source: CSR Figure X

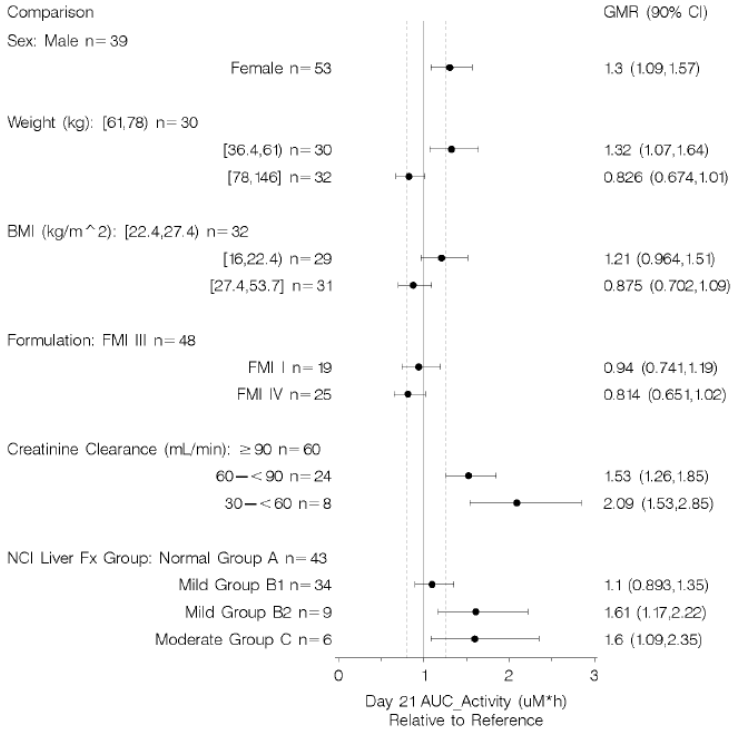
Mean T1/2 of infigratinib was approximately 7 hours longer with greater variability with moderate RI. Mean CL/F was lower (281 vs. 488 L/h). Mean non-renal clearance (CL_{NR}/F) values were similar to CL/F, indicating that renal clearance contributes very little to overall clearance of infigratinib for both groups. Less than 1% of the 125 mg dose administered was excreted as unchanged infigratinib in urine for both groups.

For CQM157 mean AUCinf was higher with moderate RI (1560 ng*h/mL) compared to healthy subjects (1170 ng*h/mL). Mean T1/2 was ~25% longer. For BHS697 the overall exposure in terms of mean Cmax and AUCs was about twice and mean T1/2 was approximately 30% longer with moderate RI. For BQR917 mean renal clearance was ~50% with moderate RI compared to HV.

In the population PK analysis creatinine clearance was found to be a statistically significant covariate on infigratinib Cl_{app} of infigratinib. Forest plots of the GMRs and 90% CIs of exposure measures for

infigratinib AUCactivity across all CCA patients in Study X2204 show that decreasing CrCL was associated with an increase in AUCactivity.

Figure PK 6 Forest Plot of GMRs (90% CI) of Covariate Effects on Overall Activity (AUCactivity) in study X2204 in steady-state



Source: Report PMX-004 Figure 48

Simulations of 1000 patients, resampled from patients in Study X2204 receiving doses of 50, 75, 100, and 125 mg daily for 21 days indicated that patients with mild or moderate RI receiving 100 mg infigratinib would achieve similar exposures to patients with normal renal function receiving 125 mg infigratinib.

Hepatic impairment

Study QBGJ398-107 investigated the PK of infigratinib in subjects with chronic mild and moderate hepatic impairment according to Child-Pugh criteria compared to 1:1 matched HV (i.e. 2 control groups, for mild and moderate HI each) from a single 125-mg infigratinib dose (5 x 25 mg capsules) as formulation FMI III under fasted conditions.

Table PK 6 Total and Unbound Plasma PK Parameters of Infigratinib

Infigratinib (BGJ398) Pharmacokinetic Parameters								
	Group A: Mild Hepatic Impairment				Group CA: Healthy Matched Subjects for Mild Hepatic Impairment			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
[a]T_{max} (h)	9	4.00 (2.00 - 4.00)			9	4.00 (2.00 - 8.00)		
C_{max} (ng/mL)	9	88.5	34.3	38.74	9	49.2	17.8	36.13
AUC_{0-t} (h*ng/mL)	9	907	591	65.12	9	487	272	55.77
AUC_{0-inf} (h*ng/mL)	9	969	741	76.48	9	497	272	54.70
AUC_{Extrap} (%)	9	3.14	5.24	166.93	9	2.32	2.20	94.82
λ_z (h^{-1})	9	0.0593	0.0255	42.97	9	0.0626	0.0301	48.09
$T_{1/2}$ (h)	9	14.2	7.37	51.93	9	13.4	5.57	41.69
T_{last} (h)	9	66.7	10.6	15.87	9	61.3	12.7	20.63
C_{last} (ng/mL)	9	1.70	3.64	214.10	9	0.484	0.282	58.30
CL/F (L/h)	9	166	61.5	37.09	9	304	118	38.62
V_z/F (L)	9	3190	2100	65.83	9	6150	3840	62.44
$C_{max,u}$ (ng/mL)	9	0.860	0.331	38.48	9	0.478	0.258	53.94
$AUC_{0-t,u}$ (h*ng/mL)	9	9.06	6.49	71.70	9	4.80	3.31	68.95
$AUC_{0-inf,u}$ (h*ng/mL)	9	9.68	8.02	82.85	9	4.89	3.32	67.94
CL/F_u (L/h)	9	17800	8280	46.51	9	36700	20900	56.93
V_z/F_u (L)	9	357000	312000	87.32	9	774000	626000	80.91
	Group B: Moderate Hepatic Impairment				Group CB: Healthy Matched Subjects for Moderate Hepatic Impairment			
Parameter	n	Mean	SD	CV%	n	Mean	SD	CV%
[a]T_{max} (h)	10	4.00 (2.00 - 6.00)			10	4.00 (2.00 - 6.00)		
C_{max} (ng/mL)	10	131	71.2	54.33	10	80.2	43.5	54.28
AUC_{0-t} (h*ng/mL)	10	1880	964	51.30	10	783	738	94.37
AUC_{0-inf} (h*ng/mL)	10	1930	979	50.61	10	804	780	96.99
AUC_{Extrap} (%)	10	2.85	2.69	94.53	10	1.98	1.81	91.35
λ_z (h^{-1})	10	0.0557	0.0224	40.22	10	0.0581	0.0296	51.05
$T_{1/2}$ (h)	10	13.8	4.34	31.35	10	14.5	5.95	40.98
T_{last} (h)	10	69.6	7.59	10.90	10	64.7	11.8	18.17
C_{last} (ng/mL)	10	2.44	1.57	64.52	10	0.917	1.75	191.08
CL/F (L/h)	10	97.6	86.7	88.76	10	231	106	45.83
V_z/F (L)	10	1800	1470	81.79	10	4970	3820	76.86
$C_{max,u}$ (ng/mL)	10	1.01	0.739	73.01	10	0.637	0.345	54.15
$AUC_{0-t,u}$ (h*ng/mL)	10	14.6	10.2	70.10	10	6.13	5.34	87.07
$AUC_{0-inf,u}$ (h*ng/mL)	10	15.0	10.4	69.18	10	6.29	5.62	89.41
CL/F_u (L/h)	10	15100	14800	98.03	10	30200	16000	53.07
V_z/F_u (L)	10	276000	252000	91.18	10	639000	541000	84.76

[a]T_{max} presented as median (range)
Unbound PK parameters: $C_{max,u}$; $AUC_{0-t,u}$; $AUC_{0-inf,u}$; CL/F_u; V_z/F_u
Note: Subjects 107-001-002 (Group A) and 107-001-008 (Group CA) were excluded from descriptive statistics.
Subject 107-001-018 (Group CA) 4.00 h protein binding results were not reportable; the 0.00 h sample was used in unbound PK parameter calculations.
Source data: Tables 14.4.4 and 14.4.5

Figure PK 7 Mean total (left) and unbound (right) infigratinib concentration-time data

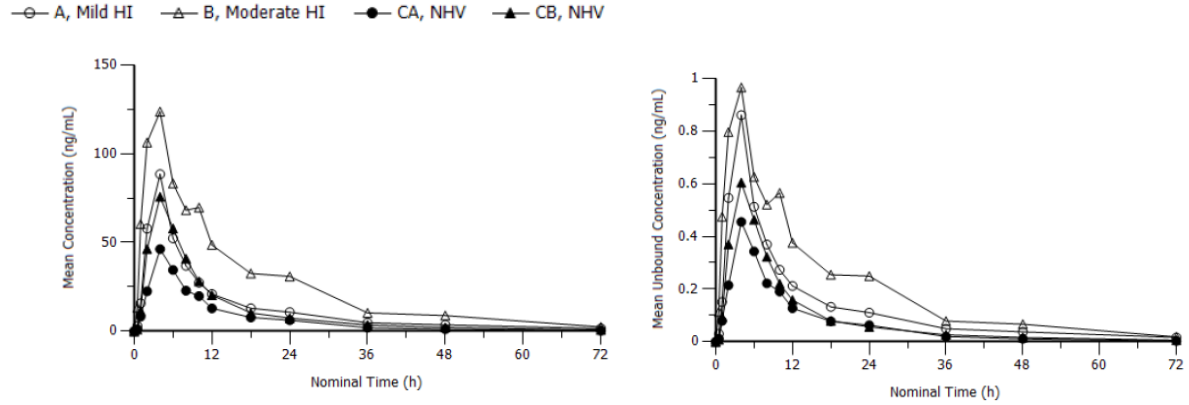
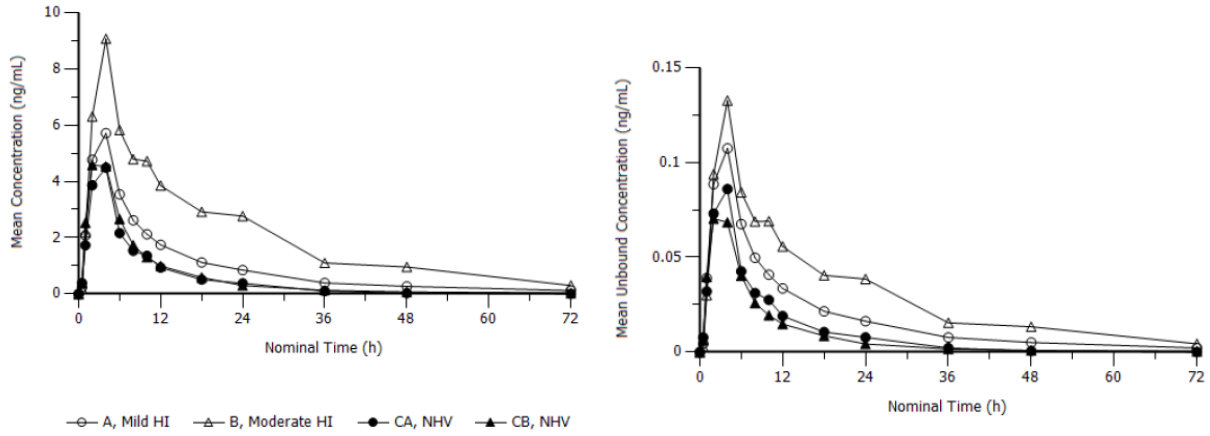
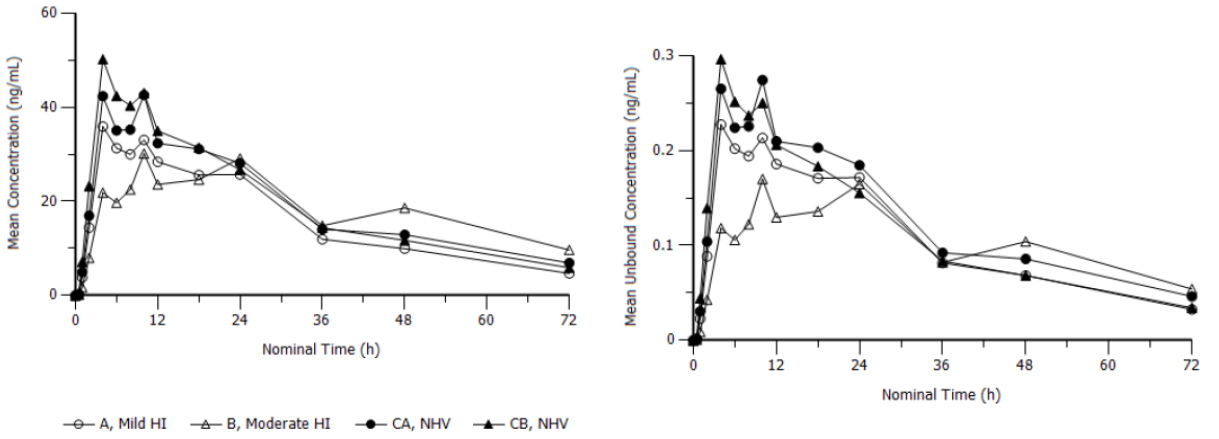


Figure PK 8 Mean total (left) and unbound (right) metabolite concentration-time data

A) BQR917



B) CQM157



C) BHS697

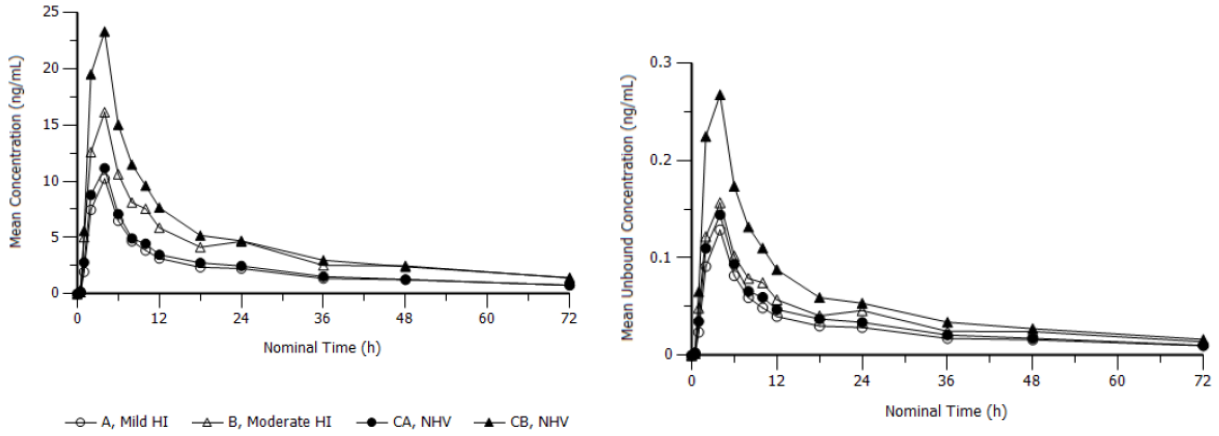


Table PK 7 Statistical Analysis of Total and Unbound Infigratinib for mild and moderate HI

	Mean (%CV)		
	Test	**Reference**	
Infigratinib PK Parameter	**Mild Hepatic Impairment (N = 9)** [a,b]	**Healthy Control (N = 9)** [b]	**GLSM Ratio (%) (90% CI)**
AUC_{inf} (h*ng/mL)	969 (76.48)	497 (54.70)	**185.56** (123.50, 278.79)
C_{max} (ng/mL)	88.5 (38.74)	49.2 (36.13)	**178.90** (133.79, 239.20)
F_u (%)[a]	0.980 (20.55)	0.915 (27.60)	--
Free AUC_{inf} (h*ng/mL)	9.68 (82.85)	4.89 (67.94)	**197.55** (118.26, 330.0)
Free C_{max} (ng/mL)	0.860 (38.48)	0.478 (53.94)	**190.46** (128.65, 281.96)
Infigratinib PK Parameter	**Moderate Hepatic Impairment (N = 10)** [b]	**Healthy Control (N = 10)** [b]	
AUC_{inf} (h*ng/mL)	1930 (50.61)	804 (96.99)	**261.54** (155.72, 439.25)
C_{max} (ng/mL)	131 (54.33)	80.2 (54.28)	**155.88** (101.15, 240.24)
F_u (%)[a]	0.734 (34.19)	0.802 (24.33)	--
Free AUC_{inf} (h*ng/mL)	15.0 (69.18)	6.29 (89.41)	**235.08** (130.68, 422.87)
Free C_{max} (ng/mL)	1.01 (73.01)	0.637 (54.15)	**140.11** (84.46, 232.43)

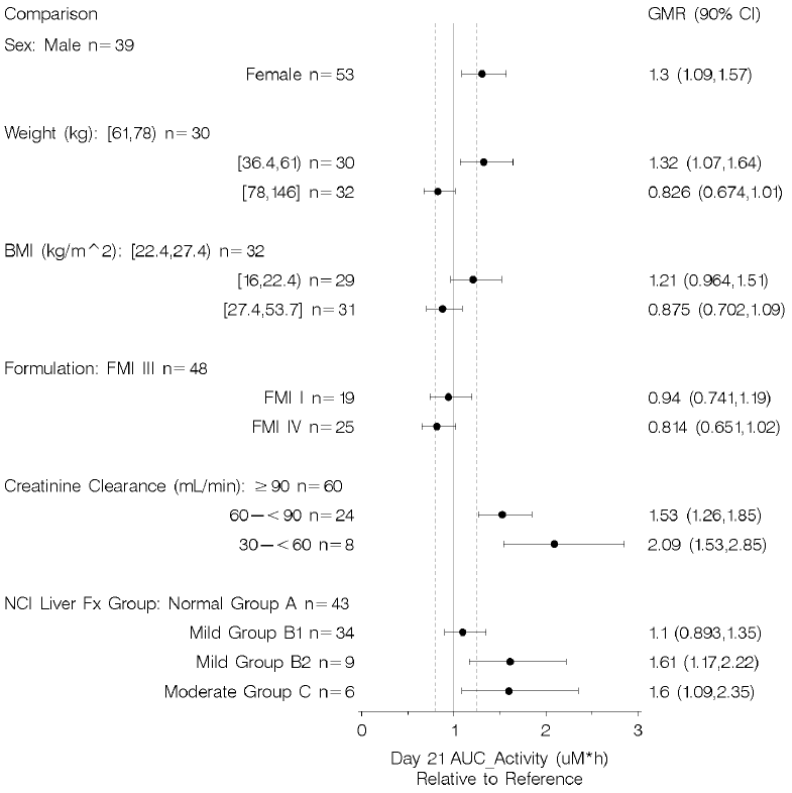
[a]Data from 1 subject was not included due to subject taking prohibited concomitant medication (omeprazole).
[b]Fraction unbound was measured at pre-dose spiked samples and at 4 h post dose. Here the 4 h fraction unbound results are reported.
Source: QBGJ398-107 CSR Tables 19, 20, 24, and 25

In PopPK report PMX-004 side-by side comparisons of the PK for mild and moderate HI categorised by Child-Pugh (C-P) from study 007 and National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria (only bilirubin and AST/ALT levels for assigning hepatic function) was performed. The reclassification of hepatic function by NCI-ODWG resulted in 5 more subjects being classified as normal (N=24) compared to C-P, 3 additional mild subjects (n=12), and significantly fewer moderate hepatic impairment subjects (n=2).

In addition, a popPK simulation of 1000 virtual patients from study X2204 (based on liver function test results of AST, ALT, bilirubin as of exclusion criterion 13) and administered simulated doses of 50, 75, 100, and 125 mg once daily for 21 days assessed HI (NCI-ODWG criteria) as a covariate. The simulations indicated that patients with mild HI (Mild B1 or B2) would achieve similar exposures with a 100 mg dose when compared to patients with normal hepatic function receiving 125 mg, while patients with moderate HI (C) would achieve similar exposures with a 75 mg dose.

PopPK report PMX-004 evaluated also covariate effects of other intrinsic and extrinsic factors. No further intrinsic factors as of gender, ethnicity, age or body weight were factors contributing relevantly to differences in PK.

Figure PK 9 Forest Plot of GMRs (90% CI) of Covariate Effects on Infigratinib AUC0-24 Overall Activity (AUCactivity) at Steady State (C) after QD Oral 125 mg in Patients With CCA



Source PMX-004 Figure 48

Pharmacokinetic interaction studies

In vitro

The nonclinical programme for infigratinib included *in vitro* studies using human biomaterials to assess metabolism and potential for DDIs.

Interaction Potential with Human Drug Metabolizing Enzymes

In vitro studies of CYP enzyme inhibition by infigratinib identified inhibitory potential of the compound for CYP3A4/5 of possible clinical relevance including a very weak time-dependent (irreversible) inhibition component. Therefore, *in vivo* evaluation of the DDI potential is warranted. The inhibitory effect of BHS697 and CQM157 on CYP enzymes is not likely to be clinically relevant. Infigratinib did not induce CYP1A2, CYP2B6, CYP2C9 and CYP3A4.

Interaction Potential with Human Drug Transporters

Infigratinib is a **substrate for P-gp and BCRP *in vitro*** and can categorised as a low-solubility, moderate permeability compound. Consequently, it **cannot be excluded that that the rate/extent of infigratinib absorption is impacted by coadministration of P-gp and/or BCRP inhibitors**. Infigratinib is unlikely to be a substrate for OATP, OAT, or OCT uptake transporters.

Infigratinib **inhibited P-gp and BCRP *in vitro***. At therapeutic doses, infigratinib is not expected to inhibit P-gp *in vivo* since 0.1*dose/250mL < IC_{50} (at intestinal level) and $I_{max,u}/IC_{50}$ <0.02 (at hepatic and renal levels) (EMA Guideline on the Investigation of Drug Interactions). In contrast, clinical interactions with sensitive BCRP probes, whose biliary elimination and/or intestinal absorption are known to be significantly promoted/limited by efflux activity, cannot be excluded. The *in vitro* inhibition of OCT1, OCT2, and MATE-2K by infigratinib is unlikely to translate into clinical significance at the therapeutic dose

based on the calculated $I_{max,u}/IC_{50}$ for these transporters being <0.02 (EMA Guideline on the Investigation of Drug Interactions). Conversely, the $I_{max,u}/IC_{50}$ for MATE1 is 0.073, and >0.02, thus**, infigratinib *in vivo* inhibition of MATE1 cannot be excluded**. Infigratinib was not found to be an *in vitro* inhibitor of OATP1B1, OATP1B3, OAT1 or OAT3.

The metabolites BHS697 and CQM157 were found to inhibit OATP1B1 and OATP1B3 *in vitro*.

Clinical studies

The effect of extrinsic factors on infigratinib PK was assessed *in vivo* in studies listed below:

Table PK 8 Clinical Studies investigating DDI of infigratinib

Study ID and Status	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Participants
QBGJ398-102	Determine effect of rifampin on PK of infigratinib and the safety and tolerability of infigratinib when administered with rifampin	Phase 1, OL, fixed-sequence, 2 treatment, drug-drug interaction Uncontrolled	Infigratinib single doses. Period 1: 125 mg infigratinib PO fasted on Day 1 Infigratinib washout: 13 days (Days 1-13) Period 2: 600 mg rifampin PO QD on Days 5-13; 125 mg infigratinib PO + 600 mg rifampin PO fasted on Day 14	Healthy Participants (N=20 enrolled and treated)
QBGJ398-103	Determine effect of itraconazole on PK of infigratinib and the safety and tolerability of infigratinib when administered with itraconazole	Phase 1, OL, fixed-sequence, 2 period, 2 treatment, drug-drug interaction Uncontrolled	Infigratinib single doses. Period 1: 75 mg infigratinib PO fasted on Day 1 Infigratinib washout: 14 days (Days 1-14) Period 2: 200 mg itraconazole PO QD on Days 12-14; 75 mg infigratinib PO + 200 mg itraconazole PO fasted, Day 15	Healthy participants (N=20 enrolled and treated)
QBGJ398-104	Determine effect of lansoprazole on PK of infigratinib and the safety and tolerability of infigratinib when administered with lansoprazole	Phase 1, OL, fixed-sequence, 2 period, 2 treatment, drug-drug interaction Uncontrolled	Infigratinib single doses. Period 1: 125 mg infigratinib PO fasted on Day 1 Infigratinib washout: 14 days (Days 1-14) Period 2: 30 mg lansoprazole PO QD on Days 11-14; 125 mg infigratinib PO + 30 mg lansoprazole PO fasted on Day 15; 30 mg lansoprazole PO QD on Days 16 and 17	Healthy participants (N=20 enrolled and treated)
QBGJ398-111	Determine effects of multiple, BID oral doses of famotidine on the PK of a single oral dose of infigratinib and the safety and	Phase 1, single-dose, OL fixed sequence, 3-period, 3-treatment, drug-drug interaction Uncontrolled	Period 1: infigratinib 4 mg, single dose PO fasted on Day 1 Infigratinib washout: 14 days (Days 1-14)	Healthy participants (N=21 enrolled (18 completed))

	tolerability of infigratinib when administered with famotidine		Period 2: infigratinib 125 mg single dose PO fasted on Day 15 Infigratinib washout: 14 days (Days 15-28) Period 3: famotidine 40 mg BID PO (Days 25-29). Infigratinib 125 mg single dose fasted on Day 29 (after the morning dose of famotidine)	
QBGJ398-106	Determine effects of multiple, QD oral doses of infigratinib on the PK of single oral doses of midazolam and the safety and tolerability of infigratinib when administered with midazolam	Phase 1, single-dose, OL fixed sequence, 3-period, 3-treatment, drug-drug interaction Uncontrolled	Infigratinib multiple doses. Period 1: single dose 2 mg midazolam PO fasted on Day 1 Infigratinib washout: 3 days (Days 1-3) Period 2: 125 mg infigratinib PO fasted overnight for 6 days (Days 4-9); single dose of 125 mg infigratinib + 2 mg midazolam PO fasted on Day 10	Healthy participants (N=20 enrolled and treated)

Effect of Other Drugs on infigratinib – infigratinib as a victim

CYP3A4 Inhibitors

Study QBGJ398-103

Exposure to infigratinib was approximately 7- and 3-fold higher for AUC_{inf} and C_{max}, respectively, when infigratinib was coadministered with itraconazole compared with infigratinib alone. Exposure to BQR917 was approximately 5.8-fold and 2.9-fold higher (AUC_{inf} and C_{max}, respectively). AUC_{inf} of BHS697 was 2.7-fold higher after coadministration of itraconazole. Mean C_{max} values for BHS697 were similar after coadministration of itraconazole, with a GMR of 0.97. Exposure of CQM157 decreased in terms of AUC_{0-t} and C_{max} with GMR of 0.60 and 0.307, respectively, but showed no change in terms of AUC_{inf} (GMR 1.08). The lack of change in AUC_{inf} may be due to the inability to determine a terminal elimination phase to estimate AUC_{inf} for some subjects.

CYP3A4 Inducers

QBGJ398-102

Mean infigratinib C_{max} and AUC values were statistically significantly lower after coadministration of rifampin. Infigratinib AUC_{0-inf} and C_{max} GMRs, were reduced by approximately 56% and 44%, respectively, during coadministration of infigratinib and rifampin. CQM157 and BHS697 exposure was reduced in the presence of rifampin. Based on GMRs, CQM157 exposure decreased by approximately 76% and 50% and BHS697 exposure decreased by 65% and 27% (AUC_{0-inf} and C_{max}, respectively). BQR917 exposure increased approximately 104% and 289%, in terms of AUC_{inf} and C_{max} with rifampin coadministration compared to infigratinib alone.

Antacids, H2 Antagonists, and Proton Pump Inhibitors

QBGJ398-104

All differences in exposure to infigratinib and its metabolites were significant (*P*<.05). Study QBGJ398-104 showed that AUC_{∞} and C_{max} of infigratinib were reduced by 45% and 49%, respectively, when infigratinib was co-administered with the proton pump inhibitor lansoprazole. T_{max} of infigratinib was delayed from 4 to 5 hours after lansoprazole. Together with the reduction in C_{max}, this indicates that the rate and extent of absorption of infigratinib is reduced with lansoprazole, leading to a corresponding decrease in AUC_{inf}. Clearance of infigratinib was significantly increased from 348 to 728 L/h. T1/2 slightly increased from 16 to 18 hours. Exposure to the metabolites was also reduced by lansoprazole, AUC_{inf} and C_{max} of CQM157 reduced by 72% and 55%; of BQR917 reduced by 31% and 24%; of BHS697 reduced by 32% and 44%, respectively.

QBGJ398-111

Study QBGJ398-111 showed that AUC_{∞} and C_{max} of infigratinib were reduced by 41% and 53%, respectively, when infigratinib was co-administered with the H2 antagonist famotidine. Clearance of infigratinib was significantly increased from 553 to 820 L/h. T1/2 only slightly decreased from 38 to 37 hours. T_{max} of infigratinib was delayed from 4 to 5 hours after famotidine. T1/2 was only slightly affected for the metabolites, resulting in extrapolated AUCs of CQM157 of 9% with famotidine vs. 11% alone, whereas no effect was seen on elimination half-life of BHS697 with 15% vs 15% and BQR917 with 10% vs. 10% AUCextrap.

Inhibitors of Transporters

I*n vitro* transporter studies indicated that infigratinib is a substrate for P-gp and BCRP. Consequently, it cannot be excluded that that the rate/extent of infigratinib absorption is impacted by coadministration of P gp and/or BCRP inhibitors. Infigratinib is unlikely to be a substrate for OATP, OAT, or OCT uptake transporters.

The potential of infigratinib to interact with transporters has not been investigated in clinical studies.

Infigratinib Effect on Other Drugs – Infigratinib as perpetrator

CYP inhibition

Study QBGJ398-106

Midazolam mean exposure was reduced by ~10% ($AUC_{0\ t}$ and $AUC_{0\text{-}inf}$) when administered after 7 days of infigratinib; no difference was observed in C_{max}. The exposure of 1-hydroxymidazolam increased by ~15%-19% in terms of $AUC_{0\text{-}t}$ and AUC_{inf} and increased ~26% in terms of C_{max}, with confidence limits outside regulatory ranges of 80-125%.

These results indicate that infigratinib had mild effect on the metabolism of midazolam. Overall, infigratinib C_{trough} increased throughout the PK sampling period, between Day 5 and Day 11. These data suggested that infigratinib is a mild inhibitor of CYP3A4. Based on these results it was concluded that the effects of infigratinib on midazolam (CYP3A4/5 sensitive substrate) metabolism were minimal and likely not clinically meaningful.

CYP induction

CYP induction has not been investigated in clinical studies. *In vitro* infigratinib was not an inducer of CYP1A2, CYP2B6, CYP2C9, or CYP 3A4.

Transporter

The potential of infigratinib to interact with transporters has not been investigated in clinical studies.

3.3.1.2. Pharmacodynamics

Mechanism of action

As outlined in the submitted Clinical Overview, among other genetic alterations, recurrent gene fusions involving the FGFRs are an important class of driver mutations in a number of tumour types, including cholangiocarcinoma (Wu 2013; Nakamura 2015). FGFR2 fusions are the most common FGFR genetic aberrations in cholangiocarcinoma (Jain 2016). FGFR fusion partners generally contain dimerisation or oligomerisation domains that lead to ligand-independent constitutive activation of the receptor and downstream MAPK-ERK and JAK-STAT signaling pathways (Touat 2015; Babina 2017), resulting in uncontrolled cell proliferation, survival, and migration, which are hallmarks of cancer. FGFR inhibition reduces cancer cell proliferation *in vitro*, decreases tumour growth in *in vivo* FGFR2 fusion-positive cholangiocarcinoma models, and has demonstrated singleagent responses in patients with cholangiocarcinoma harbouring FGFR2 fusions. Resistance can develop through mutations in FGFR2, further supporting FGFR2 fusions as a therapeutic target for molecularly selected cholangiocarcinoma patients (Lamarca 2020; Goyal 2017).

Infigratinib is a small molecule kinase inhibitor that targets FGFR1, FGFR2, and FGFR3 with *in vitro* IC50 values of 1.1, 1.0, and 2.0 nM, respectively. *In vitro*, infigratinib inhibited the activity of FGFR1-3, but not FGFR4, kinase insert domain receptor (KDR), and other kinases, at clinically relevant concentrations. The major active metabolites of infigratinib, BHS697 and CQM157, showed similar *in vitro* binding activity as infigratinib toward FGFR1-3, with similar less potent activity toward FGFR4. Infigratinib inhibited FGFR1-3 phosphorylation and signalling, and decreased cell viability in cancer cell lines with activating FGFR amplifications, mutations, and fusions that resulted in constitutive activation of FGFR signalling. Constitutive FGFR signalling can support the proliferation and survival of malignant cells. Infigratinib exhibited antitumour activity in mouse and rat xenograft models of human tumours with activating FGFR1, FGFR2, or FGFR3 alterations, including two patient-derived xenograft models of cholangiocarcinoma that expressed distinct FGFR2-fusion proteins. Infigratinib demonstrated brain-to-plasma concentration ratios (based on AUC0-inf) of 0.682 in rats after a single oral dose.

Primary and Secondary pharmacology

Non-clinical

In vitro, infigratinib inhibited the activity of FGFR1-3, less of FGFR4, but not KDR and other kinases, at clinically relevant concentrations. Infigratinib and its major metabolites BHS697 and CQM157 were shown to inhibit various targets in secondary pharmacology screens. However, based on the unbound concentrations of infigratinib and the metabolites at the recommended clinical dose of infigratinib (125 mg QD), it is unlikely that these targets would be affected.

In vivo, infigratinib significantly inhibits tumour growth in PDX models of human cholangiocarcinoma driven by distinct FGFR2 fusions.

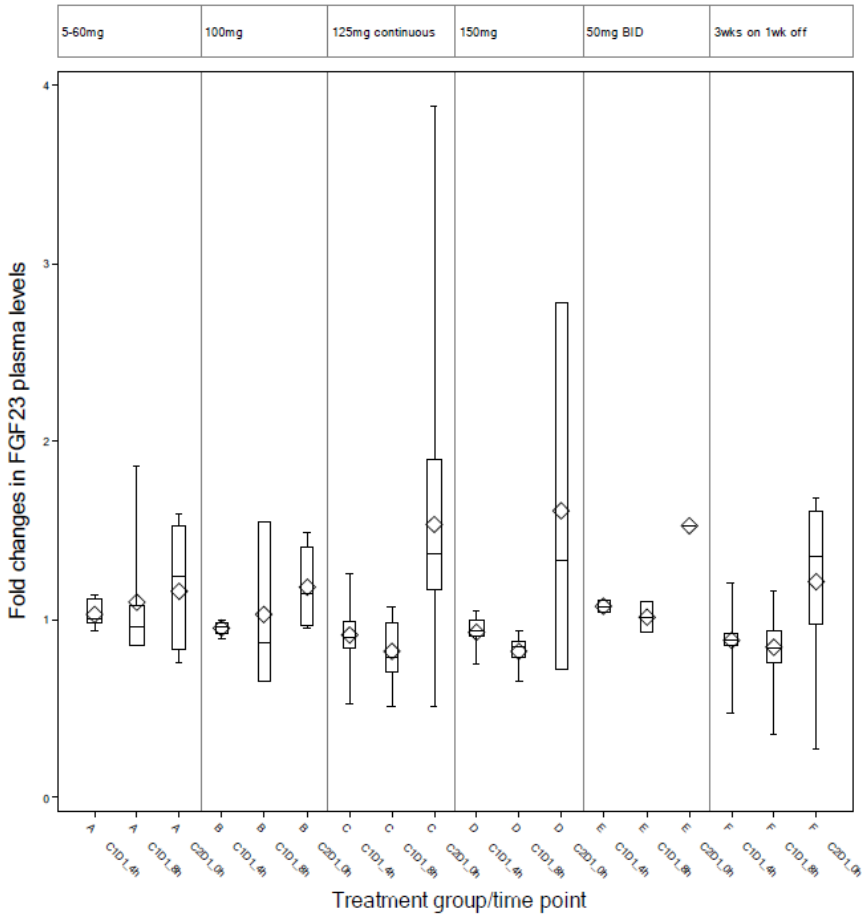
No potential for infigratinib to cause cardiovascular, neurofunctional, or respiratory effects could be identified. It is unlikely infigratinib or its major metabolites would prolong the QTc interval at clinically meaningful exposures.

Clinical

FGFR target modulation (FGF23)

As a hypothesis for measuring FGFR target modulation, FGF23 pre-and post-baseline has been measured in peripheral blood from patients in study X2101 by ELISA.

Figure PD 1 Fold changes in FGF23 plasma levels by treatment groups



Source: CBGJ398X2101, Interim Clinical Study Report, Figure 14.2-3.2, pg 208

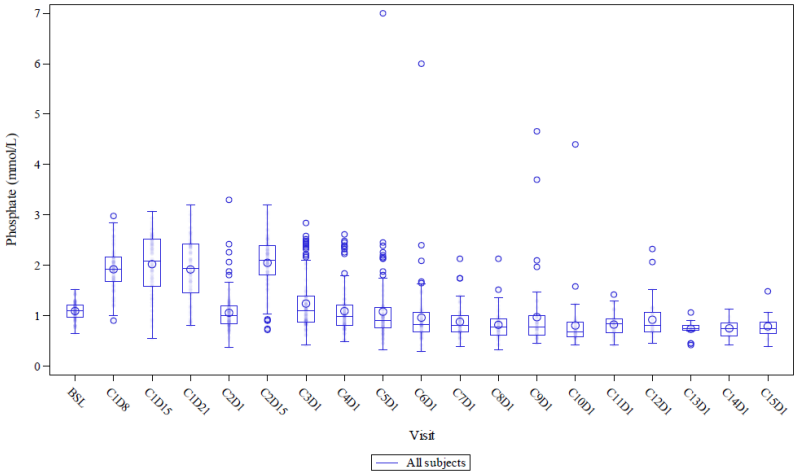
Median fold change of FGF23 from baseline to C1D1 4 hrs was 0.925, C1D1 8 hrs was 0.847, C1D2 0 hrs was 0.840, C1D15 0 hrs was 1.333, C2D1 0 hrs was 1.337, C3D1 0 hrs was 1.601.

hyperphosphataemia

Hyperphosphataemia is an expected on-target pharmacological effect of FGFR inhibition. In study CBGJ398X2101 treatment related hyperphosphataemia has been observed in 63.5% of patients.

77.8% of subjects had hyperphosphataemia in study X2204.

Figure PD 2 Box Plot of Serum Phosphate concentrations (Subjects with FGFR2 Fusion/Rearrangement in Cohort 1 FAS)



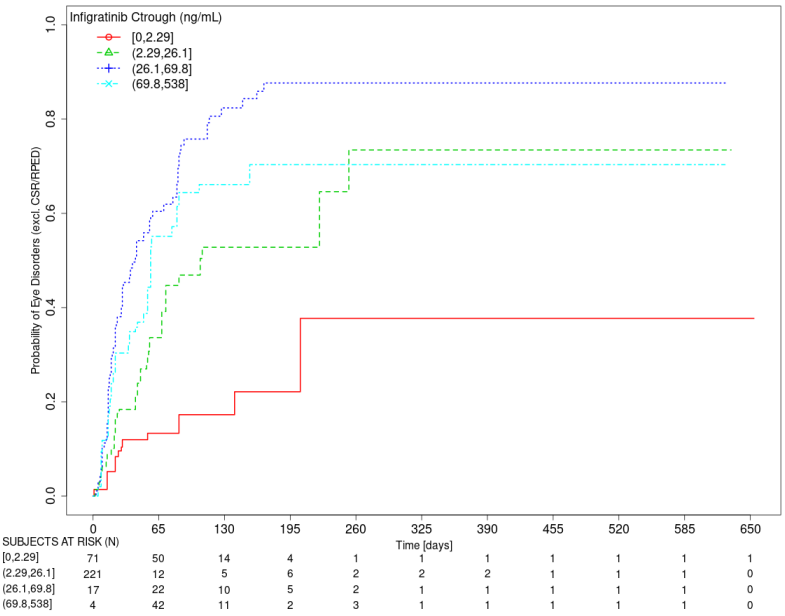
Abbreviations: FAS=Full Analysis Set; FGFR2=fibroblast growth factor receptor 2.
Only includes visits up to the last visit with ≥10 subjects with valid assessments.
Subject 5002001 has 53 mmol/L at C2D15, which is out of this chart.
Source: Figure 14.3.5.10.1

Source: Clinical Study Report CBGJ398X2204, pg 120

Eye disorders

Exploratory analysis of the overall probability of experiencing eye disorders (excluding CSR/RPED) by KM plots as shown in Figure PD 3, indicated an E-R relationship, whereby higher infigratinib exposure was associated with a higher probability of eye disorders (excluding CSR/RPED).

Figure PD 3 Kaplan-Meier Plot of Probability of Eye Disorders (Excluding CSR/RPED) Versus Time, by Quartiles of Infigratinib Ctrough



C_{trough}=plasma concentration immediately prior to dosing; CSR/RPED=central serous retinopathy/retinal pigment epithelium detachment; excl=excluding.
Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval.
Source: QED-PMX-005, Figure 18

Cardiac safety

ER analyses for QTcF did not show evidence of cardiac effects.

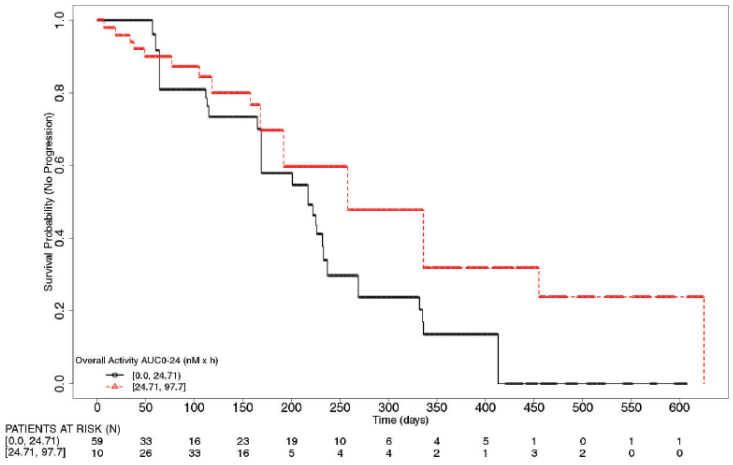
Relationship between plasma concentration and effect

Exposure-response modelling for efficacy and safety was performed by 3 models in reports QED-PMX-002, 003 and 005. Efficacy data from 69 patients from study X2204 Cohort 1 (March 2020 data cutoff) were used for the E-R efficacy analyses of PFS and 64 patients for OR. Report PMX-005 based on March 2021 data cutoff updated the results from report QED-PMX-002 for 65 patients with OR. Data from patients with advanced cancer in X1101 and X2101 (dose expansion cohorts), X2201, and X2204 were used for the E-R analysis of safety.

Efficacy

The KM curves of the probability of PFS, stratified by median exposure measures, in general, revealed no clear E-R relationship. The lower half of exposures had a similar probability of PFS compared to the higher half of exposures.

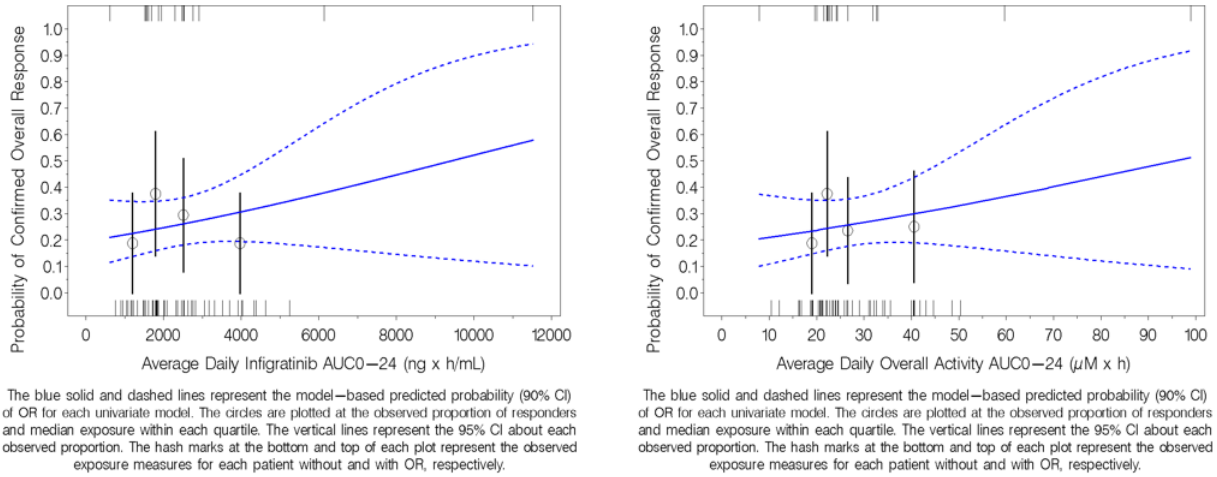
Figure PD 4 KM Plot of Probability of PFS vs Time overall activity AUC_{0-24}



Source: QED-PMX-003, Figure 7

For OR there appeared to be a dose-related incidence of OR up to 100 mg, with the response rate at 125 mg lower than the rate at 100 mg. The mean and median average daily exposure measures for the patients who experienced OR were lower as those of patients who did not. However, the range of exposures was similar in both subgroups. None of the exposure measures (Ctrough, Cmax, Cavg, and AUC0-24) evaluated were found to be statistically significant predictors ($\alpha = 0.05$) of the probability of OR. From report PMX-005, although there appeared to be a slightly positive relationship (Figure PD 5), this was not found to be statistically significant. The E-R modelling accounted for dose reductions/interruptions by determining the average daily infigratinib exposure. The lack of a significant E-R relationship may be due to the relatively small sample size of patients included in the overall analyses.

Figure PD 5 Model Predicted (90% CI) Probability of OR vs Average Daily Infigratinib AUC0-24hr and Average Daily Overall Activity AUC_{0-24hr} with Observed Data Overlaid

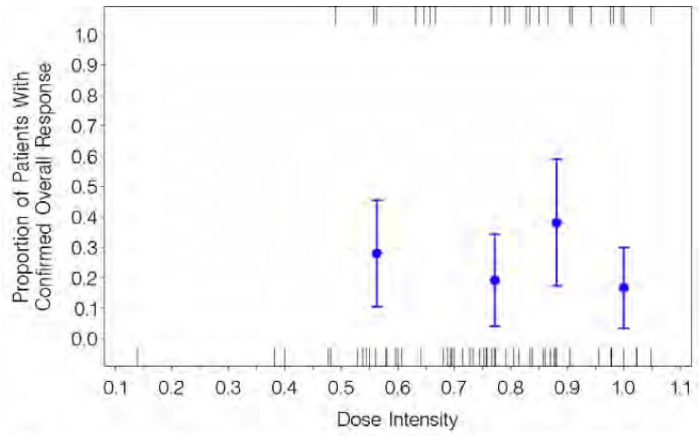


The blue solid and dashed lines represent the model−based predicted probability (90% CI) of OR for each univariate model. The circles are plotted at the observed proportion of responders and median exposure within each quartile. The vertical lines represent the 95% CI about each observed proportion. The hash marks at the bottom and top of each plot represent the observed exposure measures for each patient without and with OR, respectively.

Source: QED-PMX-005, Figure 5

Neither dose intensity nor any of the evaluated serum phosphate exposure measures (average daily serum phosphate, peak serum phosphate, and average daily serum phosphate up to Day 14) were found to be statistically significant predictors ($\alpha = 0.05$) of the probability of confirmed OR.

Figure PD 6 Observed Proportion (95% CI) of Patients With Confirmed OR vs Quartiles of Dose Intensity

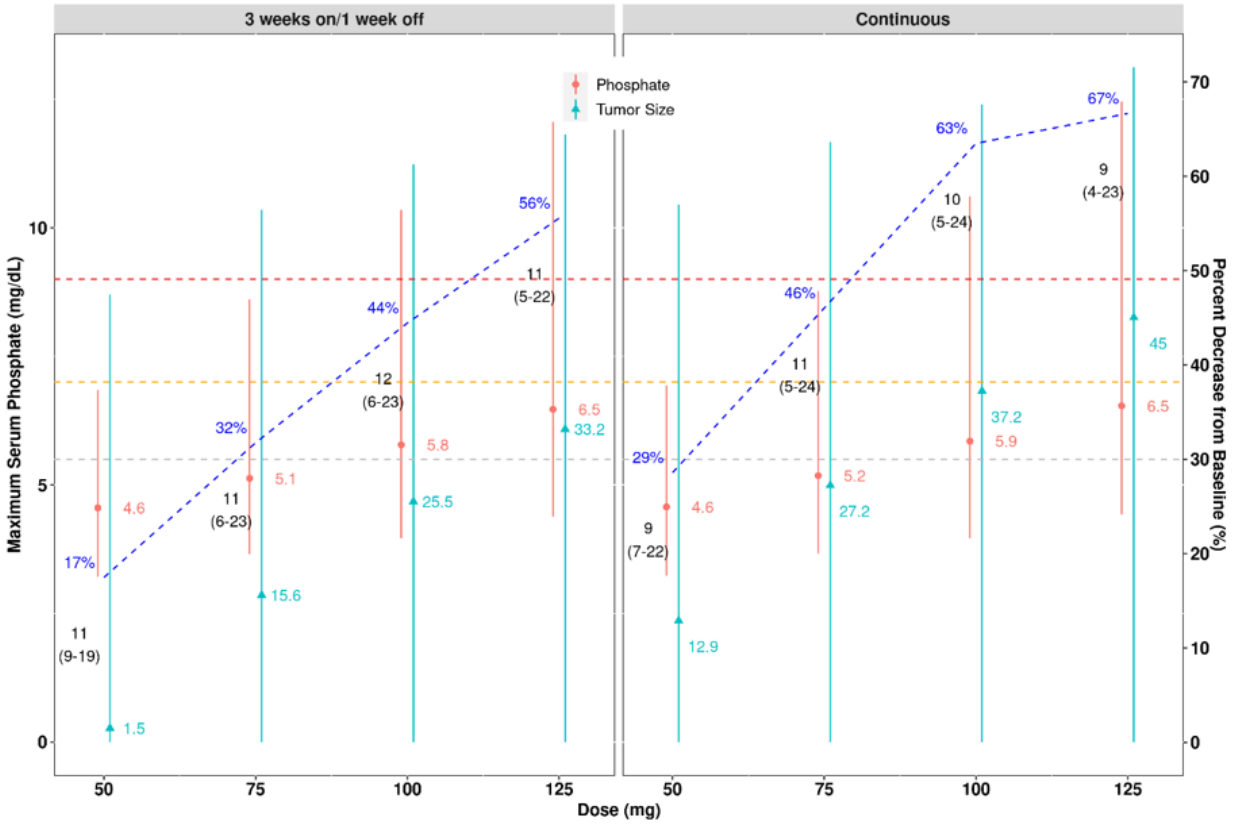


The circles represent the median exposure and associated observed proportions. The bars represent the 95% confidence interval of the proportion in each group. The hash marks at 0 and 1 represent the observed exposure measures for each patient without and with OR, respectively.

Source: QED-PMX-003, Figure 22

Stochastic simulation of 63 virtual patients from study X2204 for 2 different dosage regimens (intermittent [3 weeks on/1 week off] and continuous) and four dose levels (50, 75, 100, and 125 mg) using individual Bayesian parameter estimates from the popPK model demonstrated high variability in overall activity (%CV of ~44% in Cmax) and, hence, large overlap in overall activity between the doses was expected. In addition, the simulation of tumour size dynamics results (e.g. Figure PD 7) may represent a best case assessment since dose reductions and dose pauses were not included in these analyses.

Figure PD 7 Simulated maximum Serum Phosphate (Orange), maximum Percent Decrease from Baseline Tumour Size (Light Blue), percent of Patients with Greater Than 30% Tumour Size Reduction (Blue), and Weeks to Reach 30% Tumour Size Reduction (Black), Stratified by Dose for Intermittent Dosing (Left) and Continuous Dosing (Right)



Orange bars represent median and 90% prediction interval of the maximum simulated serum phosphate value.
Light blue bars represent median and 90% prediction interval of the maximum simulated decrease from baseline tumour size.
The blue line and text represents the proportion of patients that had a greater than 30% reduction from baseline tumour size (corresponding to PR per RECIST v1.1).
The black text represents the number of weeks to reach >30% reduction of tumour size from BL (median and range).
The orange and light blue text represent the median simulated serum phosphate and tumour size, respectively.
Horizontal dashed reference lines denote 5.5 (grey), 7 (orange), and 9 mg/dL (red) serum phosphate on the left y-axis, while the grey dashed reference line denotes a 30% reduction from baseline on the right y-axis (corresponding to PR per RECIST v1.1).
Source: QED-PMX-003 Figure 28.

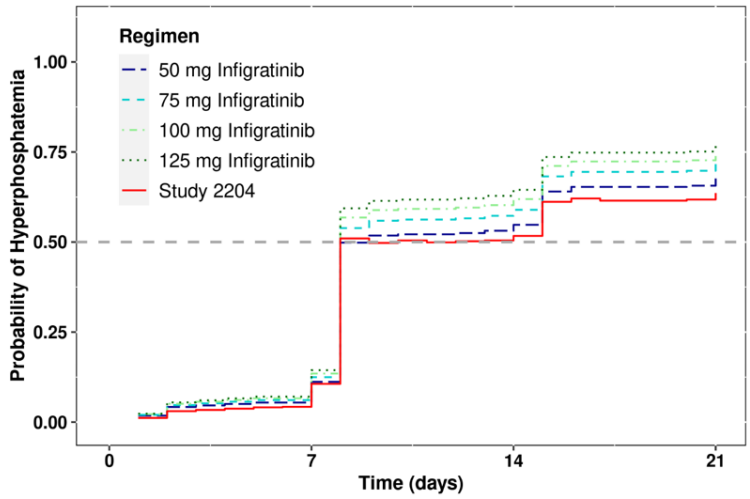
Safety

None of the evaluated infigratinib exposure measures were found to be statistically significant predictors ($\alpha = 0.05$) of the probability of first CSR/RPED. For each increase of 1 nM*h of log-transformed overall activity AUC0-24, the predicted hazard for eye disorder (excluding CSR/RPED) increased by 47%. Higher log-transformed overall activity AUC0-24 was associated with a higher risk of hyperphosphataemia, for each increase of 1 nM*h, the predicted hazard for hyperphosphataemia was increased by 59%. For both, differences were minimal (< 4% difference) between infigratinib doses of 100 mg and 125 mg

Patients receiving 125 mg infigratinib were expected to have a probability of 77% hyperphosphataemia at Day 21. While the probability for hyperphosphataemia is expected to be fairly high after the administration of 125 mg infigratinib, the median probability of hyperphosphataemia across the simulated dose range of 50 to 125 mg on Day 21 ranged from 67.6% to 77% indicating that even a

starting dose of 100 mg infigratinib (median probability of hyperphosphataemia on Day 21 of 74.6%) would only minimally mitigate the risk of hyperphosphataemia.

Figure PD 8 Simulated Probability of Hyperphosphataemia Over Time (Phosphate Binders Present, Baseline Phosphate of 3.4 mg/dL)



Note: Gray dashed line represents 50% reference line; Study 2204 represents actual exposures observed in CBGJ398X2204
Source: QED-PMX-005, Figure 24

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

The clinical pharmacology development programme for Febseltiq included 21 studies in healthy volunteers and oncology patients of which 16 relevant for the intended indication were included in popPK and modelling.

The bioanalytical methods were mainly adequately validated and it can be concluded that the methods used have adequate precision, accuracy and specificity to determine Infigratinib at the concentration levels expected in real samples for all studies. Some points have been noted on method validation. For the sensitivity problem, see the clinical discussion. The performance of the analytical methods were successfully demonstrated during in-study method performances.

All key single- and multiple-dose PK studies in HV and target oncology patient populations utilised bioanalytical methods with an LLOQ of 1.00 ng/ml for all 4 compounds. Only for the DDI, HI and RI studies and study 109 the LLOQ was 0.200 ng/ml. This hampered significantly the proper analyses of infigratinib and its active metabolites: trough concentrations, early absorption and the late elimination phases were poorly evaluable because several PK timepoints were below LLOQ, they were set to zero or missing for analyses, and accordingly all geo-mean PK parameters were only calculated from those values remaining above LLOQ, e.g. it was noted that e.g. figure 11-1 in the CSR of study X2103 seem to indicate higher geo-means than arithmetic means (which is uncommon).

Considering general requirements of the BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) for analytical methods and the large variability, a LLOQ of 1 ng/ml was mostly lower than 1/20 of the median Cmax of infigratinib, however not for the lowest Cmax, nor for all active metabolite concentrations. Admittedly, the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) states "*such a low LLOQ may be not necessary for exploratory pharmacokinetic studies*." However, proper clinical pharmacokinetic drug development including for active metabolites is an expectable key criterion.

This is considered a major oversight in the clinical pharmacokinetics development.

Based on this, the applicant should overall justify the reliability of the calculated primary and secondary PK parameters and the GLSM ratios for infigratinib and its three active metabolites both in HV and patients, under consideration of (a) the high LLOQ of 1 ng/ml in all relative BA/food effect-studies and patient studies which resulted in lots of below-LLOQ-concentrations set to zero and hence unrepresentative geo-means, (b) unsatisfactory linear regression e.g. in study 109 for some patients, (c) and the very large variability observed in all studies which is common for BCS class IV compounds.

PK of Infigratinib was described using 2-compartmental models with nonstationary (infigratinib and BHS697) or stationary (CQM157) linear elimination, first-order absorption/formation rate constant and absorption/formation lag time. Infigratinib, BHS697 and CQM157 were modelled separately. It should be clarified whether a combined (simpler) model was tested and results should be presented, when appropriate.

High inter-individual variability in the PK of infigratinib and its major circulating active metabolites could not be fully explained by the use of covariates and hampers the interpretation of the results regarding significance. The observed decrease of CL with the number of doses might be problematic with regards to accumulation – given the fact that patients achieve higher exposures compared to healthy volunteers. Until concerns regarding modelling are not addressed the dose recommendations for patients with renal and hepatic impairment should not be given based on modelling.

For infigratinib underprediction of HV data was observed. It should be clarified whether this underprediction might be the reason for the smaller predicted AUC compared to NCA results and if the alternatively tested Weibull model for absorption could lead to better results. Modelling output should be provided. To be able to assess accumulation risk during multiple dosing, additional VPCs are requested showing Patients' Multiple Dose on a time scale of 24h due to the lack of multiple dose data in HV.

Analysis of the metabolites did not always include all three moieties as during clinical development either CQM157 had not been considered relevant or BQR917. As the latter is <10% AUC of parent, this is acceptable.

In general, standard methods for non-compartmental PK analyses were utilised and the specifications if and when to evaluate lambda-z-related parameters and AUCinf or not are understandable. However, based on this methodology and due to the specific PK of infigratinib and its metabolites, in several studies in the target population no NCA elimination parameters for the metabolites were calculated.

In preclinical studies in different species the absolute BA showed a broad range and was, overall, low to moderate, indicating extensive first-pass effect. Bioavailability was also dependent on drug substance, phosphate salt or free base and formulation, solution or suspension.

Absolute bioavailability in human has not been investigated.

Permeability in Caco-2 cell was shown to be moderate due to apparent epical efflux via P-gp. The applicant claims differently in the dossier that infigratinib is a BCS class II or IV substance. For the purpose of BCS classification and in accordance with ICH M9, any drug substance that is not high permeable is classified as low permeable, resulting in classification for infigratinib as of BCS IV. This was also discussed in the Scientific Advice in 04-2019.

One of the methods to conclude on high permeability is via an absolute BA of ≥85% in accordance with ICH M9. The applicant is asked to calculate absolute BA from the available relevant clinical data (e.g. mass balance if appropriate despite the bioanalytical deficiencies in this study).

The proposed product is available in 2 capsule strengths with 25 mg and 100 mg infigratinib phosphate.

In the studies the use of the different formulations also included the use of different strengths to achieve the same dose, e.g. 5x25mg or 1x100+1x25mg. As the composition of the strengths at least for the to-be-marketed formulation FMI IV is quantitatively proportional it is appropriate to extrapolate the PK results.

Four BE studies in HV were performed comparing the FMI formulations I to III with the initial Clinical Study Formulation CSF, at single doses of 100mg or 125mg in fasted state. While FMI I and III may be considered comparable to CSF in rate and extend of absorption for infigratinib and the measured metabolites BHS697 and CQM157, based on a totality-of-data approach, the FMI II formulation was significantly less bioavailable. This resulted in stop of development of this formulation FMI II without any product having been used in patient studies.

Rate and extend of absorption were also analysed in a cross-study pooled analysis after dose-normalisation, which also included the single-dose, single-arm study 109 that evaluated PK of the formulation FMI IV in HV. Considering the large inter- and intrasubject variability for all 3 analytes, AUCinf, Cmax and Tmax may be considered comparable between the four formulations in fasted state also although not bioequivalent. This pooled analysis is the only basis for bioequivalence of formulation FMI IV in HV, in addition to popPK which also investigated formulation as covariate.

However, despite popPK report PMX-004 stated "*the effect of the to-be-marketed formulation, FMI IV, in comparison to formulations FMI I and FMI III on the PK of infigratinib, was found to have neither statistical significance nor clinical relevance*.", NCA data from study X2204 in patients suggest some exposure differences both for parent and the main metabolites both after 1st dose and in steady-state. PopPK data seem inconclusive. Hence, it remains unclear if the expose of infigratinib from formulation FMI IV is comparable between the other formulations especially with formulations FMI I and FMI III which have been used in the phase 2 efficacy study CBGJ398X2204. It is unclear how the proposed commercial formulation can be linked to the clinical formulations as no bioequivalence studies between formulation FMI IV and other formulations have been performed and the provided dissolution data is also limited and not discriminatory. Bioequivalence between the formulation used in clinical safety and efficacy studies and commercial formulation should be provided in fasting state.

Administration of the FMI III formulation with food increased exposure of infigratinib and its metabolites to 1.6- for Cmax to 2.2-fold for AUCinf, compared to CSF or FMI I in fasted state.

FMI IV was not investigated in a food-effect study. Whether the food-effect results of FMI III may be bridged to FMI IV is unknown, especially as formulation strongly affects bioavailability of BCS class IV compounds. The applicant should discuss this point, as a potential misuse by the patient, i.e. intake with food, cannot be avoided.

It was already commented in the scientific advice in 04-2019 that the applicant needs to decide whether to administer the product consistently with or without food. The applicant decided for the fasted state, which was accordingly done in the patient studies. Whether this was the most reasonable decision in view of this BCS class IV substance for which a slight reduction of variability could be observed in fed state, cannot be assessed at the time being. It would, however, have been the possibility to reduce the amount of administered drug under achievement of the same exposure.

Protein binding was high with >99% for infigratinib and metabolites. Blood/plasma ratio was 0.88. After a single dose geo-mean apparent volume of distribution of infigratinib was large in HV with up to 6830 L and lower in cholangiocarcinoma patients, after single dose 1695 L and in steady-state 3193 L, indicating extensive tissue distribution. Metabolite Vz/F was not evaluated, mainly because of incomplete concentration data for elimination phases.

In the mass balance, main routes of excretion were established as via faeces, with 77.3% in faeces and 7.22% in urine. Excretion of unchanged infigratinib was low, 3.43% of dose in faeces and 1.90% of dose

in urine, indicating extensive metabolism. Exposure after oral solution was about twice to that of the capsule formulations.

However, the mass balance study is not considered of satisfactory quality, i.e. in accordance with Appendix V of the DDI guideline CPMP/EWP/560/95/Rev. 1 Corr. 2**). Half-life of radioactivity was ~19 hours, which is longer than the T1/2 of infigratinib of ~9 hours and indicates the slower elimination rate of the metabolites. Recovery of radioactivity was below the recommended 90%, 29.5% of the recovered dose was unidentified. This might have been due to the bioanalytical problems in detection of CQM157.

In addition, Appendix V of the DDI guideline stipulates "*For drugs with dose-dependent elimination and significant accumulation under multiple-dosing, it should be considered to administer the radiolabelled single dose when steady state has been obtained with unlabelled drug. Alternatively, a supratherapeutic single dose could be used. The steady state dosing approach is also suitable if there drug has time-dependent pharmacokinetics.*" In view of the time-dependent auto-inhibitory effects on elimination and the significant accumulation, as well as the analytical deficiencies, the applicant should justify that the results of this single-therapeutic dose mass balance study are representative for characterisation of the metabolic fate and fractions obtained for infigratinib and its 3 major active metabolites.

As renal excretion of infigratinib is low, active secretion by renal transport proteins can be excluded.

From non-clinical mass balance results in dogs (report 1300099) it was discussed that enterohepatic circulation of infigratinib could be possible. The applicant is asked to discuss this aspect for its relevance in human.

Based on *in vitro* experiments, infigratinib hepatic metabolism occurred mainly via CYP3A4 (~92%) with a minor contribution by FMO3 (6%) and very minor contributions by CYP2D6 and CYP2J2.

The presented proposed 2 metabolic pathways are not in agreement as the way from BQR917 to CQM157 is once proposed and once not. For clarification and better visualisation, the applicant is asked to provide a new quantitative mass balance diagram presenting elimination pathways including the involved metabolising enzymes and transporters with percentages, as discussed in the EMA guideline "Reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (EMA/CHMP/458101/2016) based on Shepard et al., 2015. Extent of contribution of gut enzymes to first-pass metabolism was not discussed and also should be included. It might also be helpful to highlight how pathways perform when CYP3A4 is autoinhibited in steady state.

In vitro data and clinical DDI studies with itraconazole and rifampin indicated that metabolism by CYP3A4 is a major elimination pathway for infigratinib. Furthermore, infigratinib inhibited CYP3A4 *in vitro*, and significant accumulation and decreased CL/F of infigratinib were observed following repeated doses, indicating autoinhibition of elimination. In contrast, inhibition of metabolism of CYP3A4 substrate midazolam by infigratinib was not observed in the clinical DDI study QBGJ398-106. Overall, the aforementioned data suggest that 1) the design or conduct of study QBGJ398-106 was flawed (i.e., CYP3A4 is significantly inhibited by infigratinib 125 mg QD orally but this was not detected in the study), or 2) there are uncharacterised clinically significant elimination pathways for infigratinib that are subject to autoinhibition, or 3) both of the above. The applicant should discuss the potential mechanism(s) of autoinhibition of elimination by infigratinib and how they will be characterised. It is encouraged to include discussion on the effects on transporter proteins such as BCRP, given that infigratinib was *in vitro* substrate and inhibitor of BCRP.

From the 2 major metabolites with >10% AUC of parent, metabolite BHS697 contributes to 16-33%, CQM157 to 9-12% to overall activity of infigratinib at FGFR1-3 inhibition.

In vitro, the formation of BHS697 and M7 correlated well with CYP3A4/5. There was no inhibition of BQR917 formation, therefore, CYP3A4/5 is not involved in its formation. FMO3 appeared to be the major FMO isoform involved in the N-oxidation to BQR917.

It is unsatisfactory that for the 3 active metabolites, and at least for those 2 that have >10% AUC of parent, PK parameters especially of the distribution and elimination phase have only been sparsely investigated in patients, so that data for clearance, T1/2, Vz/F under dose escalation are rare. Except for the combined treatment with alpelisib in study X2102 values were mostly "not calculated". This was mostly due to the bioanalytical deficiencies with a too high LLOQ that hampered the adequate measurement of concentrations of late elimination phases and trough concentrations, therefore the remaining values that have been obtained with these analytics are regarded not giving the full PK picture. Already the CHMP recommended in the Scientific Advice that PK and elimination pathways of the active metabolites at steady state should be clarified. According to e.g. Tables 8.5. CSR X2204, the extrapolated AUC was often between 40-95% on C1D15 and terminal phase parameters were therefore not calculated. The applicant should provide a concise tabulation of the available SD and MD elimination NCA-PK data (CL/F, T1/2, Vz/F) including from dose escalation.

In study X2101, exposure to infigratinib appeared to increase more than in proportion to the dose over the dose range 5 mg to 150 mg QD which was non-significant after single dose and significant for AUC and Cmax after multiple dosing. However, at 5 mg and 10 mg doses a large proportion of the observations were BLQ. Assessment of dose proportionality over the dose range 20 mg to 150 mg QD is requested.

As metabolism of infigratinib is to ~94% via CYP3A4 the applicant is asked to provide a proportionality assessment at single and multiple dose for the active metabolites whose exposure is dependent on the extent of the concentration- and time-dependent autoinhibiton, and accordingly summarise AUCactivity.

Due to autoinhibition of its main metabolising enzyme CYP3A4, infigratinib and its metabolites BHS697 and BQR917 accumulated significantly after multiple dosing on day 15 and day 28, up to 8.9-fold. In contrast, exposure of CQM157 was reduced down to 0.5-fold in CCA patients at the proposed dose. It is noted that ratios were different depending on dose and also slightly on formulation, with highest accumulation of BQR817 at lowest dose of 50mg.

From the provided C_{trough} data from CCA study X2204 it can be estimated how accumulation develops until day 21 and how far it returns to baseline after the off-treatment week. However, more defined data were not found in the dossier. The applicant is asked to provide respective data for all four analytes and discuss how far autoinhibition of CYP3A4 can be considered resolved after the treatment pause.

Although variation of the CYP3A4 genotype contributes apparently only to a minor extent to CYP3A4 activity (e.g. Werk et al., 2014), high interpatient variability in both hepatic and intestinal CYP3A expression and function may probably be a relevant predisposing factor for the observed large inter-individual variabilities in exposure of infigratinib and its metabolites.

Also, as visible from the listings of concomitant medications in study X2101, several patients used glucocorticoids, of which e.g. dexamethasone is known to upregulate CYP3A4 mRNA expression; though, acknowledged, this may not be clinically relevant for each individual depending on the baseline enzyme activity.

The applicant is asked discuss consequences of different CYP3A4 activity and the potential of concomitant therapy for its clinical relevance in the target CCA population in view of the proposed intermittent treatment and resulting varying degree of autoinhibition. In this regard, the applicant is also asked to also discuss other potential physiological side effects of the permanent up and down of CYP3A4 efficacy by the proposed dosing schedule, in contrast to a continuous treatment with a lower dose.

In HV and patients the inter-subject variability was high for infigratinib for Cmax with 75 %CV and AUCinf 84 %CV. The intersubject variability for the metabolite exposure was moderate to high with Cmax (52-58 %CV) and AUCinf (47-77 %CV).

High variability can also be considered resultant, at least in part, from different expression levels of CYP3A4, as e.g. after enzyme inhibition by the strong inhibitor itrazonazole variability was reduced.

Under increasing doses in dose finding study X2101, exposure of infigratinib increased in an overproportional manner and also t1/2 increased. No comparably compiled PK data for the metabolites were found, neither data about Cmin. Based on data in CSR table 11-6 for day 28 it seems that D15 was not in all cases sufficient to reach steady-state. As there were PK predose samples at D16, D21, D22 and D28 the applicant should provide analysis of C_{trough} per dose to support when steady state was reached for the different doses and schedules.

For the following discussion on dose finding of the RP2D the assessor refers to the CSP amendments:

Amendment 5: *… high variability between patients in exposure has been observed and one patient experienced reversible toxicity (AST/ALT grade 3) that resulted in dose interruption and modification during cycle 1. This variability in exposure has not been observed at the lower dose level of 60 mg (q.d.) These data support further exploration of alternative dosing schedules for BGJ398, which may be assessed instead of or in parallel with q.d. dosing…*

Amendment 7: *… to Introduce an alternative dosing schedule for BGJ398 of 3 weeks on treatment followed by one week off treatment in a 3rd expansion arm […]. Results from 42 patients treated at 100 mg and 125 mg BGJ398 on a continuous once daily schedule showed drug concentrations within the predicted efficacious dose range and signs of clinical activity, i.e., tumor size reduction by CT scan. However, most of the patients treated at these efficacious doses experienced reversible toxicities (mainly hyperphosphataemia) leading to study drug interruption in the first cycle. Based on the drug administration record, the median time until first dose interruption was 22 days for patients treated at 100 mg and 21 days for patients treated at 125mg. The median days off study drug were 5 days. Furthermore, the PK results showed accumulation with multiple dosing due to auto-inhibition of clearance of BGJ398 through CYP3A4. Together, these data support further exploration of this alternative dosing schedule for BGJ398 …*

As in the X2101 dose escalation study report or study protocol no scientific rationale was given why for this targeted therapy an MTD dosing approach was considered the most appropriate, and several dose reductions already in the expansion phase could have been a hint to review the proposed dose and dosing scheme, also the PK data did not clearly indicate nor are convincing that a higher dose with higher variability would result in the most efficacious exposures with least toxicities in all patients. The rationale given especially in Amendment 7 that the new scheme was solely based on observed toxicities and treatment interruptions but in fact had no pharmacodynamic/biomarker concept, is more than scary. The applicant is asked to thoroughly justify this dose finding strategy.

Exposure of infigratinib in CCA patients was >2-fold after single dose (AUC_{0-24h} 1294 vs. 532 ng*hr/ml, Cmax 129 vs. 64 ng/ml) compared to healthy volunteers; steady state exposure has not been investigated in healthy subjects. The population PK model indicated that the apparent clearance of infigratinib was significantly lower in patients (CL_{app} -23% after adjustment for covariates).

In the dedicated RI study, generally, 7 subjects per group are considered of borderline size considering the known large variability in PK of infigratinib and its metabolites.

Despite the low fraction of drug excreted in urine, moderate renal impairment resulted in an increase of AUC of 35-58% at similar Cmax and Tmax, which was mainly due to the reduced overall clearance.

Clearance, however, was mainly affected as renal + non-renal clearance, of which the renal clearance was responsible for only 1 L/h.

Study subjects were included based on different methods of eGFR calculation: for healthy group Cockcroft-Gault (ml/min), and for renal impairment group MDRD with BSA-normalised GFR (ml/min/1.73 m^2). This resulted in subjects being out of range when calculating by each the other method. In the popPK report PMX-004, subjects of the RI study were re-calculated to ml/min and re-classified: only 5 subjects remained moderate, one changed to mild and 1 to normal (see yellow highlighting). The applicant should justify how impact of renal moderate impairment can be considered sufficiently investigated in accordance with EMA renal impairment GL (EMA/CHMP/83874/2014) requirements.

The EMA RI GL requires that primary PK parameters should also be presented on basis of unbound fraction for drug substances with high (>90%) plasma protein binding. In the CSR no evaluation of unbound PK was found, the applicant should comment and provide respective data.

PopPK evaluated a clinically relevant impact of renal function on exposure via creatinine clearance and from this the applicant proposed dose adjustments down to 100 mg /day for mild and moderate RI patients. This is principally endorsed but final conclusion can only be drawn after satisfactory responses.

SmPC section 4.2 does not state anything about eGFR or creatinine clearance as a measure for dose adjustments and section 5.2 presents study 110 results based on BSA-normalised GFR, but did not mention the 2 different methods used in the study. Both sections should be revised in accordance with the discussions. In addition, the applicant should provide supportive data, e.g. by respective modelling, how dose reductions for toxicities in patients with mild and moderate renal impairment should be performed, they should consider a new contraindication in patients with severe RI due to absence of data and provide a correspondingly amended SmPC section 4.2 and 5.2.

A dedicated HI study was performed to analyse effects of mild and moderate HI according to Child-Pugh classification after a single-dose of 125 mg FMI III.

With regard to the study design and performance, several points need to be clarified, before final conclusions from the results can be drawn:

The study recruited 2 groups of matched HV, one each to the two HI severity groups. Such a design is neither specifically supported nor disregarded by the EMA HI Guideline, which states "A within-study control group …" Please justify the rationale for 2 control groups.

It is noted that enrolment of mild and moderate HI subjects and their matching controls were nearly exclusively separated between the 2 study sites. The moderate groups were dosed after the mild groups. As there was huge difference in the PK of the 2 control groups the applicant should discuss potential reasons for these ~1.6-fold differences in Cmax and AUC (which are obviously not bioequivalent) including demographics, study site effects such as blood sampling, bioanalytics with LLOQ, or time span of recruitment considering the shelf-life expansion of the study drug to 36 months from 05-2019 to 11-2019 (for which no stability data in bottles were submitted). It should also be justified how the real effect resultant from moderate and mild HI from these different baseline data can extrapolated to a general population.

The included HI patients from Child-Pugh categories A and B did not display a broad range of the PK-relevant hepatic function parameters (bilirubin, albumin and PT/INR), as required by the EMA HI Guideline (CPMP/EWP/2339/02). Especially those included in CP-B were only of scores of 7-8, but not 9. The applicant is asked to discuss how these limitations have influenced the results and justify their conclusions for dose adjustments on this basis. As no subjects have been investigated with CP-C, patients with severe liver impairment should be excluded from treatment by a new contraindication based on lack of data.

Results indicated significant increases of exposure of infigratinib and its metabolite BQR917 in subjects with mild and moderate HI after a single dose, and less effects or lower exposure for the two metabolites BHS697 and CQM157.

On request of FDA the subjects in study 107 were re-categorised according to the NCI-ODWG criteria, which are commonly used in the US for evaluation of liver function in oncology patients. Only ALT, AST and bilirubin are used herewith, which is similar to liver function-related exclusion criteria in the main study X2204. The new grouping resulted in more subjects of normal and mild category and only 2 moderate HI subjects. Still, the resultant GMRs for mild and moderate HI are comparable to those calculated with Child-Pugh, also due to the large variability. This is acknowledged.

In addition, based on the data from CCA patients of the main phase II study X2204 exposure of infigratinib was modelled utilising the NCI-ODWG classification. On this basis the applicant proposes dose adaptions to 100 mg for mild and 75 mg for moderate HI patients to result in infigratinib exposure ranges similar to those of HI-normal patients. While this can be acknowledged, the large variability especially to higher exposures is highlighted.

In so far, and considering that in study X2204 dose reductions were frequent, the applicant should provide supportive data, e.g. by respective modelling, how dose reductions for toxicities in patients with mild and moderate hepatic impairment should be performed and provide a correspondingly amended SmPC section 4.2.

No further intrinsic factors as of gender, ethnicity, age or body weight were factors contributing relevantly to differences in PK, therefore, no dose adjustments are necessary. Treatment of children was not investigated and are not included in the current application.

Non-clinical and Clinical studies dedicated to investigating infigratinibs's potential for drug-drug interaction showed that clinically relevant interactions via CYP enzymes can be expected. Currently, this seems to be applicable more to effects of other drugs on infigratinib (as a victim) than for infigratinib effects on other drugs (as a perpetrator).

In vitro studies of CYP enzyme inhibition by infigratinib identified inhibitory potential of the compound for CYP3A4/5 of possible clinical relevance including a very weak time-dependent (irreversible) inhibition component. Therefore, *in vivo* evaluation of the DDI potential is warranted. The inhibitory effect of BHS697 and CQM157 on CYP enzymes is not likely to be clinically relevant. Infigratinib did not induce CYP1A2, CYP2B6, CYP2C9 and CYP3A4.

With regard to infigratinib as a victim, Study QBGJ398-103 showed that AUC∞ and Cmax of infigratinib were increased to 722% and 264%, respectively, when infigratinib was co-administered with the strong CYP3A4 inhibitor itraconazole. It is unclear from this single-dose study how the effect size of a strong or moderate inhibitor would affect steady-state treatment exposure. This should be discussed in view of the SmPC recommendations. The proposed text in the SmPC regarding DDI needs to be amended in accordance with responses. The advice that the coadministration of strong or moderate CYP3A inhibitors should be avoided is not adequate. If inhibitors are not to be excluded by a contraindication, dose adjustments may need to be included. No advice for weak CYP3A inhibitors is stated in the current SmPC, which also needs to be justified. Further, a newly proposed dosing regimen for strong and moderate CYP3A4 inhibitors would then need to be justified on further clinical investigations or respective modelling**.**

Study QBGJ398-102 showed that AUC0-inf and Cmax of infigratinib were reduced by approximately 56% and 44%, respectively, when co-administered with the strong CYP3A4 inducer rifampicin. It is unclear from this single-dose study how the effect size of a strong or moderate inducers would affect steady-state treatment exposure. This should be discussed in view of the SmPC recommendations.

Based on this study the SmPC states, the strong CYP3A4 inducer rifampin decreased infigratinib AUC by 56%, which may decrease the efficacy of infigratinib and consequently concurrent use of strong and moderate CYP3A inducers should be avoided during treatment with infigratinib. The advice that the coadministration of strong and moderate CYP3A4 inducers is not recommended is not adequate. If inhibitors and inducers are not to be excluded by a contraindication, dose adjustments may be needed. No advice for weak CYP3A inducers is stated in the current SmPC, which needs to be justified. Given that infigratinib exhibits complex time-varying PK, dose finding strategy for infigratinib was questionable, and CYP induction usually takes place gradually over 1-2 weeks, the applicant is asked to discuss potential dosing regimens for infigratinib used concomitantly with mild, moderate and strong CYP3A4 inducers.

Study QBGJ398-104 showed that AUC∞ and Cmax of infigratinib were reduced by 45% and 49%, respectively, when infigratinib was co-administered with the proton pump inhibitor lansoprazole and by 41% and 53%, respectively, when infigratinib was co-administered with the H2 antagonist famotidine. It is unclear from this single-dose study how the effect size of a proton pump inhibitor or H2 antagonist would affect steady-state treatment exposure. This should be discussed in view of the SmPC recommendations. Based on results of these studies overall, plasma exposure of infigratinib is affected when infigratinib is co-administered with pH modulators such as PPIs or histamine 2 (H_2)-receptor antagonists. The dose adjustments as described in the SmPC needs to be further justified.

In DDI study QBGJ398-106, the effect of infigratinib on CYP3A4 was investigated with midazolam as a victim drug. The median Tmax and T½ for midazolam were 0.5 h and 2.9 h indicating that midazolam was very rapidly absorbed and rapidly eliminated. Infigratinib PK was not characterised in the study, except for pre-dose drug samples. However, it is known that infigratinib is poorly soluble at intestinal pH and its absorption is relatively slow. For example, in healthy volunteers in study QBGJ398-107 the infigratinib median Tmax was 4.0 h (range: 2.0 – 8.0 h) following ingestion of the same dose and formulation that was used in study QBGJ398-106 [125 mg (5 x 25 mg capsules); FMI III formulation]. Furthermore, this DDI study carried out at the early time point of day 7 has probably not revealed the full steady-state inhibition during treatment and leaves it hence unclear to what maximal extent infigratinib treatment inhibits CYP3A4 clinically and affects the exposure of substrates in long-term treatment.

In view of the intermittent dosing scheme the applicant should discuss whether the maximal inhibitory effect of infigratinib on CYP3A4 at intestinal level and at systemic level was captured in study QBGJ398-106, given the different solubility and absorption kinetics of midazolam syrup and infigratinib capsules. In addition, it should be justified that one study after 7 days of infigratinib 125mg dosing is sufficient to characterise clinical CYP3A4 inhibition for infigratinib as a reversible and irreversible (time-dependent) inhibitor, and in accordance with the EMA DDI GL recommendations. The applicant's interpretation of the results as minimal and not clinically meaningful can currently not be supported.

CYP induction has not been investigated in clinical studies.

Information with regard to interaction based on potential CYP inhibitors (inducers) is missing in section 4.5. The SmPC should be amended.

Infigratinib was *in vitro* a substrate of both P-gp and BCRP. Clinical DDI studies with inhibitor of P-gp and inhibitor of BCRP should be performed to characterise their effects on the PK of infigratinib and its major metabolites, unless the applicant can scientifically justify why such studies would not be necessary.

The clinical relevance of the infigratinib's potential to inhibit MATE1 and BCRP substrates has not been evaluated in a dedicated clinical drug interaction study. The applicant is requested to perform a clinical study to investigate DDI for MATE1 and BCRP inhibition or to justify why such studies where not performed.

Also amendment of several sections of the PI is requested, see commented PI document.

Pharmacodynamics

No definite information was provided by the applicant, neither in the non-clinical nor in the clinical documentation where and how binding of infigratinib occurs and what the result of binding is: e.g., binding at the extracellular domain(s) in competition to physiological ligand as a receptor-antagonist; binding at the intracellular site(s) for auto-phosphorylation, for ATP, in the kinase domain; whether conformational changes are expected. This is considered missing relevant data and should be submitted.

In vitro, infigratinib inhibited the activity of FGFR1-3, less of FGFR4, but not KDR and other kinases, at clinically relevant concentrations. Infigratinib and its major metabolites BHS697 and CQM157 were shown to inhibit various targets in secondary pharmacology screens. However, based on the unbound concentrations of infigratinib and the metabolites at the recommended clinical dose of infigratinib (125 mg QD), it is unlikely that these targets would be affected.

In vivo, infigratinib significantly inhibits tumour growth in PDX models of human cholangiocarcinoma driven by distinct FGFR2 fusions. No potential for infigratinib to cause cardiovascular, neurofunctional, or respiratory effects could be identified. It is unlikely infigratinib or its major metabolites would prolong the QTc interval at clinically meaningful exposures.

Connection of FGF23 increase and inhibition of FGFR signalling was presupposed by the applicant. While on day 1 of treatment an initial decrease of FGF23 levels might be observed, especially at doses ≥100mg, a weak dose response can be seen for the increasing continuous dose groups until C2D1, however with large variability in effect size. After the 7-days treatment pause (right column) it can be seen that effect size is returned to lower levels. No data were available to show how the FGF23 plasma levels increase until day 21, to show that the desired effect was obtained prior to the drug pause at the proposed dose scheme. The applicant should discuss this and provide corresponding data.

Results of exploratory endpoints as well as further PD investigations of a clinical proof-of-concept, such as inhibition of autophosphorylation of FGFR2, were not found and should be presented and discussed.

ER analyses for QTcF did not show evidence of cardiac effects.

The applicant should discuss the possibility of pharmacodynamic interactions that are conceivable for infigratinib. This should include PD interactions at target and off-target structures, independently from PK.

The population of CCA patients with FGFR2 rearrangements or fusions treated with infigratinib were not further investigated for differences in pharmacodynamic response based on genetic differences. The applicant should discuss possible differences in pharmacodynamic response based on genetic differences. This discussion should include secondary FGFR2 mutations acquired during infigratinib treatment as resistance mechanism, as referenced by the applicant e.g. in Goyal et al., 2017.

Overall, exposure-response analyses did not indicate any significant relationship for efficacy measures of PFS or OR and exposure, neither for infigratinib or its metabolites alone nor for overall AUC activity, which included the activity of the metabolites.

In contrast, adverse reactions were dose/exposure dependent, although e.g. for hyperphosphataemia the general probability was high, so that even a dose of 50mg would not lead to a relevant reduction.

The applicant simulated 4 doses (50, 75, 100 and 125mg, intermittent and continuous, without including dose holds and reductions) to support the proposed dose and scheme. It is obvious that for all simulations the effects are highly overlapping, and no definite advantage of the 125mg intermittent 3w on/1w off scheme becomes evident.

The most interesting figure in this regard is nevertheless the overlay of efficacy (tumour size reduction and time to achieve a PR) and safety (phosphate-related) parameters. While error bars are large and

any conclusion of a more positive B/R ratio of one dose over another can only be deemed speculative, it seems that tumour size dynamics as of time to achieve a PR are quite independent of dose with 11-12 weeks (black figures). Considering that in study X2204 the mean relative dose intensity was 78% (32% with 75 mg and 24% with 100 mg intermittently) that it can then be derived from that simulation that the final effect size is similar to ~75mg given continuously.

3.3.3. Conclusions on clinical pharmacology

The overall performance and presentation of the clinical pharmacokinetic development programme is considered of unsatisfactory quality.

The weaknesses concern, at least, the bioanalytical methods with too high LLOQ, unsatisfactory quality of the mass balance study, 5 different formulations for a BCS IV drug substance of which the final to-be-marketed FMI IV has unclear bioequivalence and food-effect, large variability at least due to auto-inhibition of the main metabolising pathway via CYP3A4, evaluation of the primary and secondary PK parameters for at least 2 of 3 active metabolites in all relevant studies, design of the dedicated RI and HI studies, and finally, dose finding based on MTD and "dose interruption observations" for a targeted drug substance without a pre-defined proof-of-concept of a potential efficacious exposure.

The latter is believed a clinically relevant concern because the inhibition and recovery of the CYP3A4 pathway could become a problem also for other physiological procedures beyond metabolism of the proposed drug and its drug interactions.

Key DDI studies were performed, however the effect sizes of single-dose infigratinib may not be fully representative for and extrapolatable to steady-state drug treatment. Furthermore, DDI studies addressing interactions related to tranporter proteins should be carried out, unless the applicant can justify otherwise.

As regards PD investigations, except of a weak dose response od FGF23 increase at doses ≥ 100mg in continuously dosed groups until C2D1 in study X2101, though with large variability in effect size, no further PD investigations of a clinical proof-of-concept, such as inhibition of autophosphorylation of FGFR2, were obviously performed. Results of several exploratory PD endpoints were not found. Such data should be presented and discussed.

Overall, there are general methodological shortcomings in the clinical pharmacokinetics/-pharmacology development, including at least different formulations with formulation- and compound-immanent PK factors like pronounced food-effect, enormous variability in exposure that was lower e.g. at 60 mg vs. 125 mg in the dose finding study and concentration-dependent autoinhibition of the main metabolising pathway, without any E-R relationship for efficacy but for safety.

3.3.4. Clinical efficacy

Infigratinib is an inhibitor of the FGFR family of receptor tyrosine kinases (FGFR1, FGFR2, and FGFR3). The purpose of the current submission is to seek marketing approval for infigratinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

Clinical studies that support efficacy claims in cholangiocarcinoma are presented below. The study CBGJ398X2204 *is the pivotal and only study supporting the efficacy of infigratinib in this application*

Study ID; # of Study Centres; Location	Study Objectives; Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s)[a]; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
5.3.5 Reports of efficacy and safety studies							
5.3.5.1 Study reports and related information of controlled clinical studies pertinent to the claimed indication (Not Applicable)							
5.3.5.2 Study reports and related information of uncontrolled clinical studies							
CBGJ398XUS04 41 USA	Assess clinical benefit (CR, PR, SD, OR, PFS, OS, DOR), safety and tolerability Clinical benefit rate (CR, PR, or stable disease ≥16 weeks for solid tumours)	Phase 2, OL, signal-seeking Uncontrolled Completed (70-90 subjects planned) 21JUL2014	Infigratinib 125 mg PO QD: 3 weeks on / 1 week off (28-day cycles)	85 enrolled 84 treated 37M/47F 60.2 (33-85) years	Solid tumour or hematologic malignancy or with a history/ evidence of TIO and FGF23-mediated hypophosphataemia with or without identification of an FGFR genetic alteration	28-day cycles until disease progression, study termination, or other DC reason	Complete; CSR
CBGJ398X2204 18 USA, Germany, Thailand, Singapore, Spain, Belgium, Taiwan	Determine efficacy (ORR, PFS, BOR, DOR, OS), safety and PK of infigratinib and PK of FMI III and FMI IV ORR by BICR	Phase 2, multicentre, single arm Uncontrolled Ongoing (160 subjects planned across all cohorts) 23JUL2014	Infigratinib 125 mg PO QD: 3 weeks on / 1 week off (28-day cycles) Formulations FMI I, FMI III, and FMI IV	108 Cohort 1 subjects with FGFR2 fusions enrolled and treated as of 31MAR2020 cutoff date 41M/67F 53.4 (23-81) years	Advanced or metastatic CCA with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy	28-day cycles until disease progression, study termination, or other DC reason	Ongoing; Interim CSR
See above	See above	See above	See above	108 Cohort 1 subjects with FGFR2 fusions enrolled and treated as of 01MAR2021 cutoff date 41M/67F 53.4 (23-81) years	See above	See above	Ongoing; Primary CSR (pivotal)

Abbreviations: BA=bioavailability; BICR=blinded independent central review; BID=twice daily; BOR=best overall response; CCA=cholangiocarcinoma; CR=complete response; CRC=colorectal cancer; CSF=Clinical Service Form; CSR=clinical study report; CSR/RPED= central serous retinopathy/retinal pigment epithelium detachment; DC=discontinuation; DCR=disease control rate; DOR=duration of response; ECG=electrocardiogram; E-R=exposure-response; FGFR=fibroblast growth factor receptor; FMI=Final Market Image; Loc=location; MTD=maximum tolerated dose; NA=not applicable; NR=nonrandomised; OL=open-label; OR=overall response; ORR=overall response rate; OS=overall survival; PD=pharmacodynamic; PFS=progression-free survival; PK=pharmacokinetic(s); PO=oral; PR=partial response; QD=once daily; QOL=quality of life; QT=interval in an ECG test of heart function; QTc=duration of the QT interval adjusted for the subject's heart rate; QTcF=QTc using Fridericia correction; R=randomised; SD=stable disease; TE=treatment-emergent; TIO=tumour-induced osteomalacia; Tx=treatment; UCC=urothelial cell carcinoma; WT=wild type; XO=crossover.

[a] Nomenclature for the investigational product has evolved over the development programme. The current convention is to refer to the Final Market Image followed by the appropriate formulation by Roman numeral (ie, FMI I, FMI II, FMI III, FMI IV). This terminology is used with the exception that the protocol title remained unchanged.

3.3.4.1. Dose-response studies

The CBGJ398X2204 dose and dosing regimen of 125 mg QD of infigratinib on a 3 weeks on (21 day)/1 week off (7 day) schedule in 28-day cycles was based on safety, efficacy, and PK modeling during the dose escalation phase of the Phase 1 CBGJ398X2101 trial in 34/39 patients with advanced solid tumours (confirmed advanced solid tumours carrying any FGFR mutation, amplification or gene fusion, for whom no effective standard therapy exists).

For PK-Modeling, data from 34 of the 39 subjects (not including subjects on the twice daily regimen) enrolled in the dose-determining set were analysed. Using the Bayesian Logistic Regression Model assessment results along with the escalation with overdose control principle, and review of all available safety information, including dose-limiting toxicity data, PK data, and pharmacodynamic (PD) data, the maximum tolerated dose was determined to be 125 mg once daily on a continuous dosing schedule. However, this dose regime was obviously not tolerable and the applicant evaluated an alternative dosing schedule, ie, 3 weeks on/1 week off, at 125 mg QD during dose expansion part of the same study, aiming to reach a better tolerability. From this preliminary data and modelling results the 3 weeks on/1 week off 125 mg QD schedule was declared as the recommended Phase 2 dose and used in trial CBGJ398X2204.

However, even with this posology, overall, 65.7% of subjects had a reduction in dose due to any reason; 34.3% of subjects had no dose reduction. The lowest dose reduction levels were 75 mg/day (32.4%), 100 mg/day (24.1%), 50 mg/day (8.3%), and 25 mg/day (0.9%) (CBGJ398X2204 Primary CSR Section 12.1.2). AEs that led to dose adjustment in ≥10% of subjects were hyperphosphataemia (25.9%) and stomatitis (12.0%). Since dose reduction levels of 75 mg/day (32.4%) or 100 mg/day (24.1%) were most frequently needed, this dose range may be more adequate and may probably allow continuous treatment within this dose range. It seems that overall most patients were exposed longest with this dose range in the pivotal trial CBGJ398X22204. Thus applicant is requested to discuss and reject the thesis that a lower dose should be used; in particular since it seems that for the confirmative trial for the CMA the same posology is used and similar dose reductions can be foreseen.

E-R and PK/PD modeling of efficacy endpoints, namely tumour response, confirmed OR and PFS, and various safety endpoints were performed to assess infigratinib exposure measures as a predictor of efficacy and safety, however the reliability of this analyses is not convincing due to the low quality of the underlying data.

3.3.4.2. Pivotal study

Efficacy evaluation for infigratinib in the applied indication for the *treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement* is based on a **retrospective assessment from subjects in Cohort 1 with FGFR2 gene fusions or other rearrangements enrolled in Study CBGJ398X2204.**

Study: Study CBGJ398X2204

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*

This study is an ongoing multicentre, open-label, 3-cohort, Phase 2 study, which evaluates infigratinib antitumour activity in advanced or metastatic cholangiocarcinoma subjects in Cohort 1 with FGFR2 genetic alterations.

All subjects receive oral infigratinib administered once daily for the first 3 weeks (21 days) of a 28-day treatment cycle. Study drug is continued until disease progression, unacceptable toxicity, withdrawal of consent, or death.

Results focus on subjects with FGFR2 fusion/rearrangement in Cohort 1. Once study drug is discontinued, subjects complete an End of Treatment (EOT) Visit, followed by 30-day Safety Follow-up Visit.

Thereafter, subjects who discontinue study drug for any reason other than disease progression have tumour assessments every 8 weeks until disease progression or the initiation of subsequent antineoplastic therapies, or death, whichever occurs first. All subjects are being followed for survival at least every 4 months after discontinuation of study drug. Survival follow-up continues for up to 5 years or until all subjects discontinue the study, die, withdraw consent, or are lost to follow-up.

Documented evidence of FGFR gene alterations is required for all subjects in Cohort 1. The specific genetic alterations allowed are 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 FGFR gene fusions**.

Furthermore, with protocol amendment 2, enrollment was restricted to subjects with cholangiocarcinoma **harboring FGFR2 fusion/rearrangement** (?).

In addition, the formulation of infigratinib was changed from FMI I to FMI III.

Both of these formulations were taken by subjects in Cohort 1 and are included in this report. 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.

Protocol amendment 4 specified **2 additional cohorts, Cohort 2 and Cohort 3**.

- **Cohort 2** allows **additional FGFR genetic alterations** (other than FGFR2 fusions) and excludes subjects with prior or current FGFR inhibitor or MEK inhibitor therapy.
- **Cohort 3** allows **only FGFR2 fusions** and **requires prior treatment with a FGFR inhibitor other than infigratinib.**

Moreover, 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 centre.

Study and Reporting period:

Date first subject treated: 23 July 2014

Date of data cutoff: 01 March 2021

Methods

Study Participants

Main inclusion criteria:

- Histologically or cytological confirmed cholangiocarcinoma at the time of diagnosis. Subjects with cancers of the gallbladder or ampulla of Vater are 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 (focus of this Application).** (**Note: Cohort 1 mainly consists of FGFR2 fusions; however, other genetic aberrations were allowed in Cohort 1 before protocol amendment 2.)**

Not included in this application

• *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 [X2204-Appendix 16.1.1] (for mutations not listed in Appendix 4, enrollment may be allowed with written pre-approval of the QED medical monitor).

• *Cohort 3: FGFR2 fusions* (must receive prior treatment with an FGFR2 inhibitor).

- 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 evidence of progressive disease after their prior regimen; if prior treatment was discontinued due to toxicity, subjects must have had continued evidence of measurable disease.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1 (Subjects with ECOG PS of 2 may 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 is not allowed, with the exception of Cohort 3 (protocol amendment 4), which requires prior FGFR2 inhibitor therapy.

Locations

The study was conducted across 20 study centres that enrolled subjects (9 in the US, 3 in Germany, 2 in Singapore, 2 in Thailand, and 1 each in Belgium, Spain, Korea, and Taiwan).

Treatments

Subjects receive **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 are being 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 is 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 centre**.

Batches of infigratinib (for subjects in Cohort 1 included in the analysis) were supplied from formulations FMI I, FMI III and FMI IV.

Treatment duration: Study drug is being continued until disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, or death.

Objectives

Primary objective

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 objectives

The secondary objectives are:

- To further evaluate the efficacy of single agent infigratinib (Cohort 1).
- To characterise 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 characterise the pharmacokinetic (PK) profile of infigratinib Final Market Image (FMI) III and FMI IV formulations (overall study).

Exploratory Objectives

- To characterise 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).
- 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 (Cohort 3).
- To assess markers that may correlate with genetic alterations in tumour tissue at baseline, predictions of response and/or resistance (e.g., gene mutations, amplifications, deletion and/or altered protein expression or activation) (overall study).

Outcomes/endpoints

Primary endpoint

The primary endpoint of this study is to determine the 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 endpoints

- Overall response assessed by investigator; progression-free survival (PFS), best overall response (BOR), disease control assessed by investigator and by BICR according to RECIST 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 endpoints:

- 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 (tumour tissue) from subjects who progressed and analysis of cell free deoxyribonucleic acid (cfDNA) (overall study).
- Serial serum CA19-9 levels (overall study).

Sample size

At the time of the interim analysis, the interim efficacy analysis set was to include 72 subjects with FGFR2 gene fusions. The half-width of the exact 95% confidence interval for ORR was not to exceed 12%.

With at least 106 subjects with FGFR2 gene fusions, this sample size was to result in the exact 95% confidence interval half-width of ORR less than 10%.

Randomisation and blinding (masking)

This application is based on a retrospective analysis of data from a single arm, open-label study without randomisation.

Statistical methods

The Statistical Analysis Plan (SAP) is dated 13 May 2020 and a supplementary SAP, dated 08 April 2021, specified additional analyses for the final CSR.

Data in this MAA submission are from the third formal interim analysis of Cohort 1. The primary analysis of the primary endpoint (ORR assessed by BICR) included subjects in Cohort 1 with FGFR2 gene fusions or other rearrangements who had received ≥1 dose of infigratinib (subjects with other FGFR alteration FAS (N=14) comprised the remaining subjects from Cohort 1).

For Cohort 1, one analysis was performed before Protocol Amendment 2 based on the 61 subjects enrolled in the study (30 Jun 2016). Protocol Amendment 2 restricted enrollment to subjects with FGFR2 fusions, and the formulation was changed from FMI I to FMI III. After 20 subjects had been treated with FMI III (for at least one cycle) based on Protocol Amendment 2, a comprehensive review of all relevant data such as PK, safety, dose interruptions/reductions/intensity, and available efficacy was performed. In addition, 2 formal interim analyses for Cohort 1 were planned after Protocol Amendment 3. The first formal interim analysis for Cohort 1 was conducted when all subjects in the Interim Efficacy Analysis Set 1 had been followed for at least 10 months after their initial exposure to the study treatment. The second formal interim analysis for Cohort 1 was planned when all subjects who received infigratinib at the time of the first formal interim analysis after amendment 3 had at least 10 months follow-up after their initial exposure to infigratinib.

For the subgroup of subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS enrolled under protocol amendment 2 or a subsequent amendment, key efficacy summaries were repeated. (The reason for this subgroup analysis is the enrollment to Cohort 1 was restricted to the subjects whose tumours had FGFR2 fusions/rearrangement starting from amendment 2. Before that, the study could be considered hypothesis generating, and after that, the study could be considered hypothesis confirming).

ORR (central imaging assessment) is the primary efficacy endpoint, and its analysis consists of a Clopper-Pearson 95% CI accompanied by a characterisation of time to response (TTR) and duration of response

(DOR) to allow for a more complete characterisation of the beneficial effect infigratinib may have in the principal analysis population.

Exact 95% CIs were also provided for secondary response endpoints.

Response onset and DOR were summarised for confirmed responders only and were done separately based on BICR and investigator assessment. Response onset was defined as the time from the first study treatment administration date to the initial response date. DOR was defined as the time from the initial response to the date of the event defined as the first documented progression or death due to any cause, whichever was earlier. DOR was analysed using Kaplan-Meier (KM) product limit method. The same event/censoring rule applied to PFS was applied to DOR. The Brookmeyer-Crowley method was used to construct the 95% CI for DOR.

PFS was defined as the date of the start of treatment to the date of the event defined as the first documented progression or death due to any cause, whichever was earlier. If a subject had not had an event, PFS was censored at the date of the last valid tumour assessment or start of study treatment if there was no valid tumour assessment available. Subjects who had an event after 2 or more missed visits were censored at the last adequate tumour assessment. PFS analyses were done separately based on BICR and investigator assessment. KM analysis of PFS was performed. The primary PFS was derived based on all the tumour assessments and death including any after a subsequent antineoplastic therapy. A sensitivity analysis was conducted on PFS, excluding the tumour assessments and death after any subsequent antineoplastic therapies.

OS was defined as the time from the date of start of treatment to the date of death due to any cause. The survival time for subjects without documentation of death before the data cut-off was censored at the last date the subject was known to be alive before the cut-off date. Survival time for subjects with no post-baseline survival information was censored at the date of start of treatment. OS was analysed using the KM method.

Results

The data cutoff date for this interim analysis was 01 March 2021, with the data snapshot taken on 13 April 2021 and back-filtered to keep only data up to 01 March 2021.

The Full Analysis Set (FAS) includes all subjects in Cohort 1 (N=122).

For this CSR, FAS is further split into the following 2 groups:

- Subjects **with FGFR2 fusion/rearrangement in Cohort 1** FAS: **108 subjects**

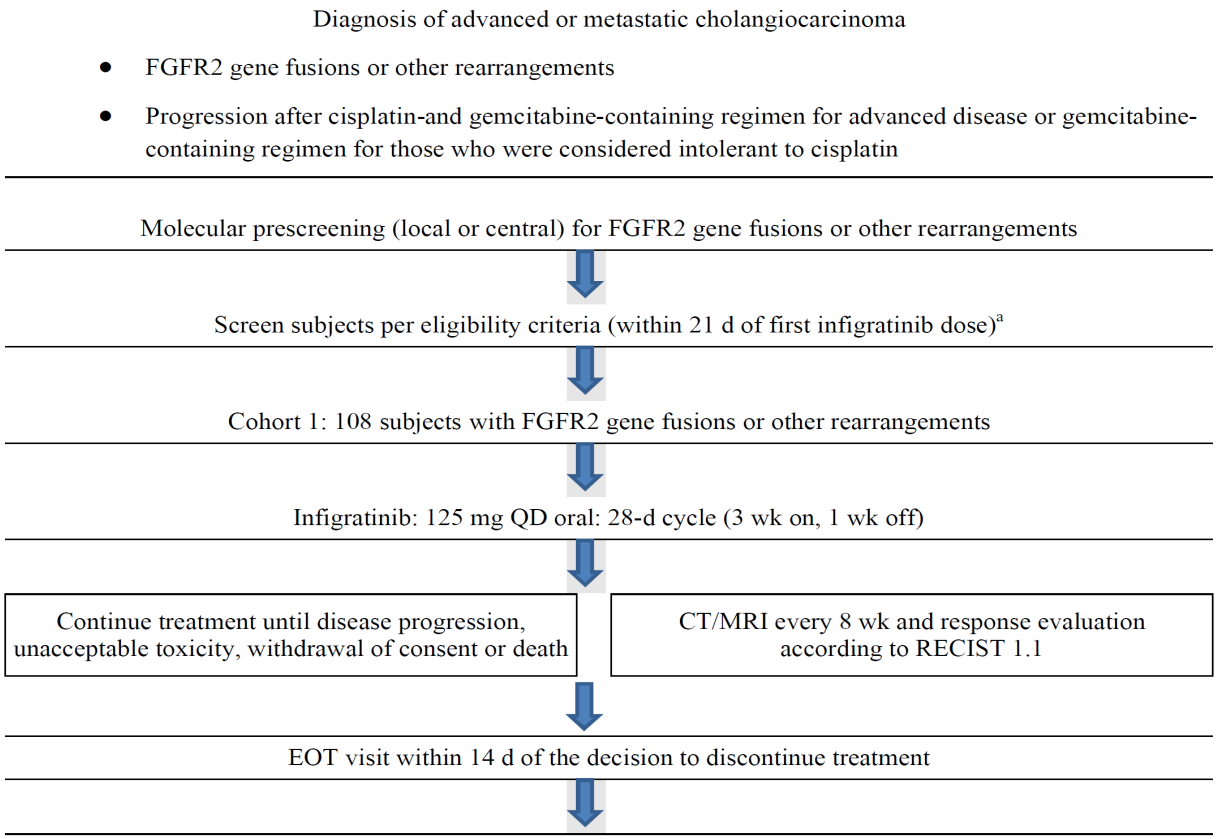
  These are the same 108 subjects as the main dataset presented in the interim CSR [X2204] ("Interim Analysis Set 2 for Cohort 1"); the only difference in the data is the length of follow-up ("subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS" in this CSR have 11 months more follow-up than the "Interim Analysis Set 2 for Cohort 1" from the interim CSR).

- Subjects **with other FGFR alteration in Cohort 1** FAS: **14 subjects**

  These subjects include 12 enrolled before protocol amendment 2 was implemented and 2 enrolled under permission by the sponsor (Novartis) after implementation of amendment 2.

Results are only discussed for subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS (N=108), and in-text presentations focus solely on this group.

Participant flow



CT=computed tomography; d=day; EOT=end of treatment; FGFR2=fibroblast growth factor receptor 2; mo=month; MRI=magnetic resonance imaging; RECIST=Response Evaluation Criteria in Solid Tumors; Wk=week.
Screening assessments were completed within 21 days before the first dose of treatment, except for the radiological tumor assessment, which could be performed within 28 days before the first dose.
Source: Modified from CBGJ398X2204 Primary CSR, Figure 1

The applicant is requested to provide an adequate diagram illustrating the participant follow in the pivotal trial X2204 for efficacy. This should better illustrate than the current figure reflecting the number of patients screened, included, excluded and detail the reasons for exclusion in the main analysis in order to get a comprehensible overview on one glance.

Moreover, a second diagram is requested with the same intention for the "all subjects 125 mg monotherapy –safety target population" which additionally includes also patients treated for other indications, but relevant for the evaluation of the safety outcome in the non-primary safety population (N=363 subjects).

Recruitment

The studied period is reported as from (first subject treated: 23 July 2014 to 01 MAR 2021 (data cut-off date). Information regarding the recruitment in the trail is missing. Thus, the applicant is requested to provide an overview regarding the chronology of recruitment in the pivotal Cohort 1 of trial Study CBGJ398X2204 and regarding the time in trial according outcome (CR, PR, Stable disease and Death).

Conduct of the study

6 Amendments were performed (latest: Revised based on updates to standards for safety and study conduct for infigratinib; and **added second interim analysis on 15 Jan 2020**).

For Cohort 1, the first interim analysis was performed before protocol amendment 2 based on the 61 subjects enrolled in the study (see Table 1, Javle 2018b).

Protocol amendment 2 restricted enrollment to subjects with FGFR2 fusions, and the formulation was changed from final market image (FMI) I to FMI III. Introduction of the FMI III formulation to this study was supported by a relative bioavailability study (Clinical Service Form [CSF] vs FMI III) in healthy subjects (CBGJ398X2106) and a pooled analysis of FMI III vs FMI I ([X2204-Appendix 16.1.13] [pooled analysis FMI III vs FMI I]). It was observed that there was an increase in exposure of FMI III compared to FMI I if administered at the same dose level (21% for AUCinf, 29% for Cmax, and 35% for AUClast). This difference was not considered clinically relevant, and further PK data was collected in the first 20 patients in this study.

After 20 subjects had been treated with FMI III (for ≥1 cycle), a comprehensive review of all relevant data (e.g., PK, safety, dose reductions) was performed. The safety and tolerability data from the first 20 subjects treated with FMI III, up to the end of Cycle 1 of treatment, was assessed and compared with the historical data from subjects treated with FMI I (data on file). Upon review of the data, FMI III appeared to pose no additional safety concerns; observed events were readily monitorable and considered manageable, and it was decided to continue dosing all subsequent subjects with FMI III, at 125 mg, on a 3-weeks on, 1-week off schedule.

In addition, 2 formal interim analyses for Cohort 1 were planned after protocol amendment 3 (see also Table 1):

• **First formal interim analysis for Cohort 1 after protocol amendment 3**: A formal interim analysis for Cohort 1 was conducted after all subjects in the Interim Efficacy Analysis Set 1 for Cohort 1 had been followed for ≥10 months after their initial exposure to the study drug. Efficacy analysis for this interim analysis was based on the Interim Efficacy Analysis Set 1 for Cohort 1, with some key efficacy analyses repeated in the Full Analysis Set (data on file).

• **Second formal interim analysis for Cohort 1 after protocol amendment 3**: The interim CSR [X2204] presents this interim analysis, which was conducted after all subjects who received infigratinib at the time of the first formal interim analysis had the potential for ≥10 months follow-up after their initial exposure to infigratinib. This interim analysis was based on Interim Analysis Set 2 for Cohort 1 and Sensitivity Analysis Set for Cohort 1.

Baseline data

For cohort 1, the median age was 53.0 years old and the majority of participants were under 65 years of age (82 patients, 75.9%). Patients of 85 years of age and older were not represented. The majority of the patients were female (67 patients, 62.0%), from North America (77 patients, 71.3), white (78 patients, 72.2%), and had ECOG performance status of 0 (45 patients, 41.7%) or 1 (62 patients, 57.4%). The majority of patients had normal renal function or a mild renal impairment at baseline (65.7% and

26.9%, respectively) and normal hepatic function or a mild hepatic impairment at baseline (49.1% and 46.3%, respectively). Almost all patients had a carcinoma of the bile duct (106 patients, 98.1%). 102 (94.4%) had metastatic sites, the most common extrahepatic metastatic sites of disease were lung (74 patients, 68.5%) and lymph nodes (62 patients, 57.4%) and bone (28 patients, 25.9%).

Allmost all of the patients (n= 107, 99.1%) presented an advanced stage disease (stage IV) at baseline and one patient was included with stage I (0.9%).

In accordance with study eligibility criteria, all participants had advanced/metastatic. At baseline, the majority of the patients had received one prior therapy administered in the metastatic/advanced setting (42 patients, 38.97%), whereas 2 prior therapies or 3 or more had been administered to 35 patients (32.4%) and 16 patients (14.8 %) respectively. 15 patients (13.9%) had even ≥4 prior therapies.

Nearly all subjects (96.3%) had progressed on ≥1 prior regimen. Of these, 95 subjects (88.0%) had progressed on a gemcitabine-based regimen; 1 subject received prior carboplatin and paclitaxel but is included for completeness within the "gemcitabine-based therapy" category. The remaining 13 subjects (12.0%) discontinued gemcitabine for toxicity, with 9 of these subjects progressing on another regimen before initiating infigratinib. Subjects were considered to have progressed on or after prior gemcitabine-based therapy if ≥1 prior gemcitabine-based therapy was ended due to disease progression (or best response was noted to be disease progression) or reason for ending prior gemcitabine-based therapy studies was not due to an adverse event (AE) or toxicity. It seemed that in difference to other clinical studies the number who had received platinum compounds at baseline was relatively low. Considering the efficacy of these compounds the applicant should explain the reasons and discuss the impact of this approach regarding outcome.

41.7% of subjects had undergone prior antineoplastic surgery. Median time from last surgery to first day of study drug was 15.2 months (range: 1 to 57 months). The most common surgical procedures were hepatectomy (25.0%), cholecystectomy (6.5%), and lymphadenectomy (4.6%); 16.7% had residual disease at last surgery. Moreover, 75.0% of subjects had not received prior radiotherapy. Within the 25.0% of subjects who did receive prior radiotherapy, the most common locations of radiotherapy were the liver (37.0%), bone (29.6%), and other locations (not specified) (37.0%); the setting of last radiotherapy was palliative/therapeutic (74.1%), neo-adjuvant/adjuvant (22.2%), or other (7.4%).

Although it is acknowledged that the applied subtype of FGFR2 cholangiocarcinoma is mostly intrahepatic (Jain et al 2019), the applicant is requested to clarify the number of patients with intra –and extrahepatic disease (ICC/ECC) and report the outcome for both groups separately in order to differentiate whether outcome is comparable in both subtypes.

Furthermore, the applicant is requested to provide an overview regarding the identified FGF/FGFR Genetic Alterations Identified by Central Genomics Laboratory in the study population at the time of inclusion and report whether other concomitant genetic alterations beside the target mutation were also identified in the included population.

The mean treatment compliance among subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS was 77.6%; this is rather low for a clinical trial in oncology and thereby may indicate difficulties in tolerability of the provided posology. Considering that in Pemigatinib the compliance was about 100 % the question has to be raised, whether the "3 week one week off" scheme (compared to 2 weeks on and 1 week of in pemigatinib) may be less tolerable than the shorter treatment with pemigatinib which additionally resulted in a higher ORR rate than with infigratinib.

Numbers analysed

Up to approximately **160 subjects are planned for enrolment**, with approximately 120 subjects in Cohort 1, approximately 20 subjects in Cohort 2, and up to approximately 20 subjects in Cohort 3.

A total of 108 subjects with FGFR2 fusion/rearrangement were included in Cohort 1 FAS; of these, 101 subjects (93.5%) were included in the PPS. Seven subjects (6.5%) were excluded from the PPS for not being evaluable for efficacy (6 subjects) and/or for having a protocol deviation of not meeting protocol inclusion criteria (3 subjects). No separate analyses were conducted on the PPS because <10% of subjects were excluded from subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS, as specified in the SAP.

Outcomes and estimation

Assessment by BICR:

Primary Endpoint:

Objective Response Rate Assessed by BICR

The **primary endpoint (ORR assessed by BICR)** was **23.1%** (95% confidence interval [CI]: 15.6, 32.2) including **1 subject with a confirmed CR** and 24 subjects with confirmed PR (Table OE 1).

The K-M estimate for median DOR assessed by BICR was 5.55 months (95% CI: 3.78, 7.66), with the longest duration of 19.12 months.

Nine subjects (36.0%) had DOR ≥6 months, 4 subjects (16.0%) had DOR ≥9 months, and 1 subject (4.0%) had DOR ≥12 months.

Table OE 1: Summary of Efficacy Results by BICR and Investigator (Cohort 1 FAS With FGFR2 Fusion/Rearrangement)

	Assessment of Disease by	
	BICR	**Investigator**
Primary Endpoint, n	108	NA
Objective Response rate[a] n(%)	25 (23.1)	
(95%CI)[b]	(15.6, 32,2)	
Secondary Endpoint, n	NA	108
Objective Response rate[a] n(%)		35 (32.4)
(95%CI)[b]		(23.7, 42.1)
Duration of response c, n Kaplan-Meier estimate	25	35
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)
Response onset, n	25	35
Mean (SD), 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
Confirmed CR, n (%)	1 (0.9)	0
Confirmed PR, n (%)	24 (22.2)	35 (32.4)
Stable disease d, n (%)	66 (61.1)	56 (51.9)
Unconfirmed CR/PR, n (%)	14 (13.0) e	10 (9.3)
Progressive disease, n (%)	11 (10.2)	11 (10.2)

Table OE 1: Summary of Efficacy Results by BICR and Investigator (Cohort 1 FAS With FGFR2 Fusion/Rearrangement)		
	Assessment of Disease by	
	BICR	**Investigator**
Not done, n (%)	6 (5.6)	6 (5.6)
Disease control rate f, n	108	108
Event, n (%)	91 (84.3)	91 (84.3)
(95% CI) b	(76.0, 90.6)	(76.0, 90.6)
Progression-free survival g, n	108	108
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, n	108	
Death event, n (%)	89 (82.4)	
Median (95% CI) b, months	11.86 (10.68, 14.85)	

BICR=blinded independent central review; CI=confidence interval; CR=complete response; max=maximum; min=minimum; NA=not applicable; PR=partial response; SD=standard deviation.
+ indicates numbers reported for subjects whose response is still ongoing.

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

b Binomial proportion with exact 95% CI.

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

d Non-CR/nonprogressive disease considered stable disease for subjects who only have non-target lesions at baseline.

e All 14 subjects with unconfirmed response discontinued the study as of the data cutoff of 01 March 2021. Of these 14 subjects, 9 subjects discontinued for disease progression per investigator's assessment, 4 subjects discontinued for adverse events, and 1 subject discontinued for physician decision.

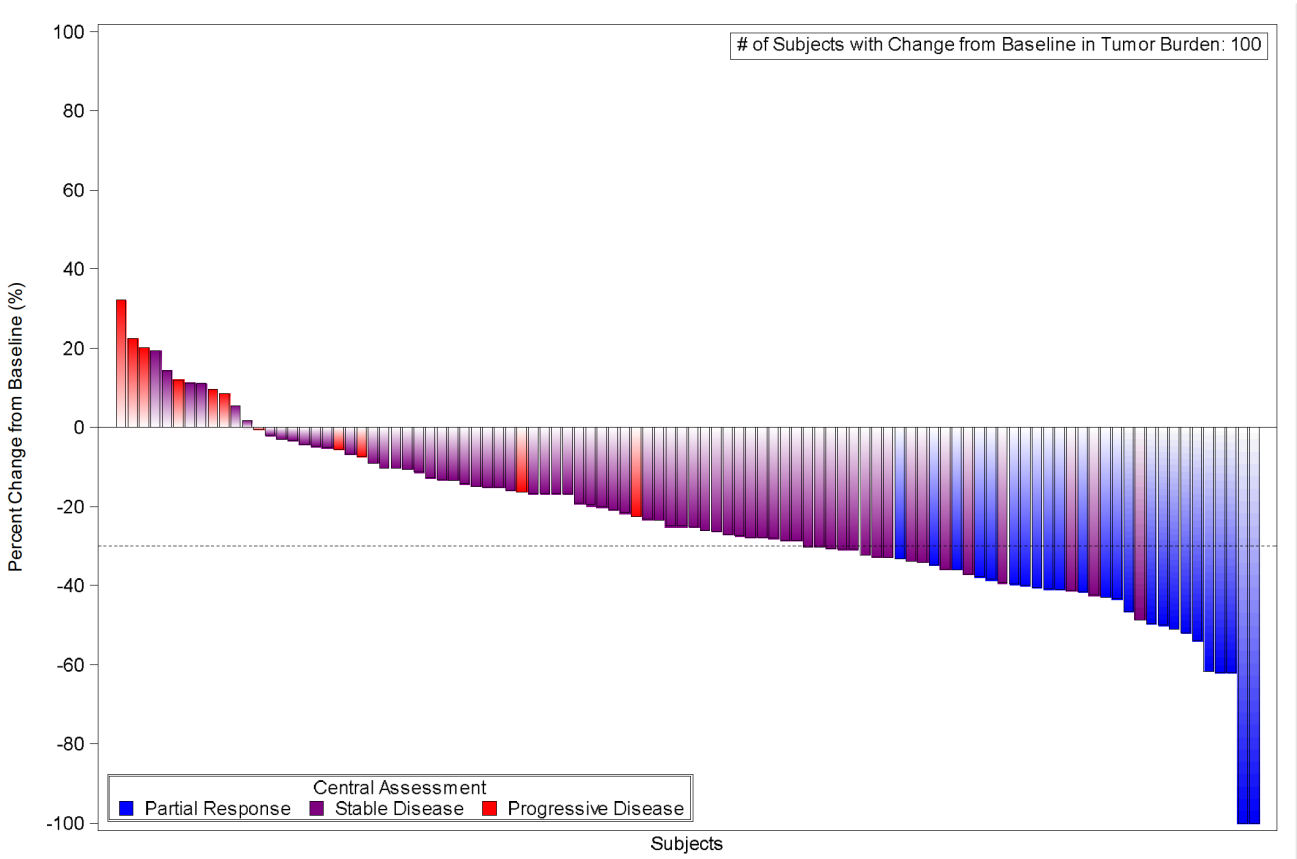
f Subjects with best overall response as confirmed CR, PR, or stable disease (including unconfirmed CR/PR).

g 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 tumour assessment. For subjects who had an event after ≥2 missed visits, the subject was censored at the last adequate tumour assessment before the missing visit.

Data cutoff date: 01 March 2021.

Source: CBGJ398X2204 Primary CSR Table 15

Figure OE 2: Waterfall Plot of Maximum Percentage Reduction in Tumour Burden with Best Overall Response Assessment by BICR (Cohort 1 FAS With FGFR2 Fusion/Rearrangement)



BICR=blinded independent central review.
N=100 in this figure; 6 subjects did not have an assessment, and 2 subjects did not have measurable disease.
Data cutoff date: 01 March 2021.
Source: CBGJ398X2204 Primary CSR Figure 2

Primary Endpoint: Objective Response Rate Assessed by BICR

The **primary endpoint (ORR assessed by BICR)** was **23.1%** (95% confidence interval [CI]: 15.6, 32.2) **including 1 subject with a confirmed CR** (?) and **24 subjects with confirmed PR** (Table 6). **The K-M estimate for median DOR assessed by BICR was 5.55 months (95% CI: 3.78, 7.66), with the longest duration of 19.12 months.**

Secondary Endpoint: Objective Response Rate Assessed by the Investigator

In difference to the BICR assessment of efficacy, the secondary endpoint of ORR assessed by the investigator was significantly higher **32.4%** (95% CI: 23.7, 42.1), with a median DOR of 7.23 months (range: 1.51+, 20.70) (Table 6). A total of 15 subjects (42.9%) had DOR ≥6 months, 9 subjects (25.7%) had DOR ≥9 months, and 2 subjects (5.7%) had DOR ≥12 months.

Secondary Endpoint: Best Overall Response

The secondary endpoint of BOR assessed by BICR was confirmed CR (0.9%), confirmed PR (22.2%), stable disease (61.1%), and progressive disease (10.2%) (Table OE 2).

Table OE 2: Best Overall Response Assessed by Investigator Versus BICR (Cohort 1 FAS With FGFR2 Fusion/Rearrangement)						
Best Overall Response Assessed by Investi-gator, n (%)	**Best Overall Response Assessed by BICR, n (%)**					
	Confirmed CR	**Confirmed PR**	**Stable Disease**	**Progressive Disease**	**Not Done**	**Total**
Confirmed CR	0	0	0	0	0	0
Confirmed PR	1 (0.9)	17 (15.7)	17 (15.7)	0	0	35 (32.4)
Stable disease a	0	7 (6.5)	46 (42.6)	3 (2.8)	0	56 (51.9)
Progressive disease	0	0	3 (2.8)	8 (7.4)	0	11 (10.2)
Not done, n (%)	0	0	0	0	6 (5.6)	6 (5.6)
Total	1 (0.9)	24 (22.2)	66 (61.1)	11 (10.2)	6 (5.6)	108

BICR=blinded independent central review; CR=complete response; PR=partial response.
a Non-CR/non-progressive disease was considered as stable disease for subjects who only had non-target lesions at baseline.
Data cutoff date: 01 March 2021.
Source: CBGJ398X2204 Primary CSR Table 19

Both subjects in the waterfall plot (Figure 2) with 100% target lesion reduction achieved confirmed PR but had persistent non-target lesions (data on file).

BOR assessed by the investigator was confirmed CR (0%), confirmed PR (32.4%), stable disease (51.9%), and progressive disease (10.2%) (Table 6).

Within the 66 subjects (61.1%) who had stable disease per BICR, 14 subjects (13.0%) had unconfirmed CR/PR by BICR (1 subject with unconfirmed CR who proceeded to a planned resection of metastatic lesion and discontinued study treatment before confirmation of response; 13 subjects with unconfirmed PR).

All 14 subjects with unconfirmed response discontinued as of the data cutoff of 01 March 2021. Of these 14 subjects, 9 subjects discontinued for disease progression per investigator's assessment, 4 subjects discontinued for AEs, and 1 subject discontinued for physician decision.

A total of 5 subjects developed new bone lesions while on infigratinib treatment; 4 of these 5 subjects were allowed to continue on study treatment beyond progression due to new bone lesions, at the request of the investigator based on an assessment that the subjects continued to derive benefit. All 4 subjects were tolerating study treatment, and 3 of these had some reduction in the size of visceral target lesions, before the development of new bone lesions.

Tumour response with treatment exposure is presented in Figure OE 3.

Figure OE 3: Tumour Response and Treatment Exposure with Assessment by BICR (Cohort 1 FAS With FGFR2 Fusion/Rearrangement)

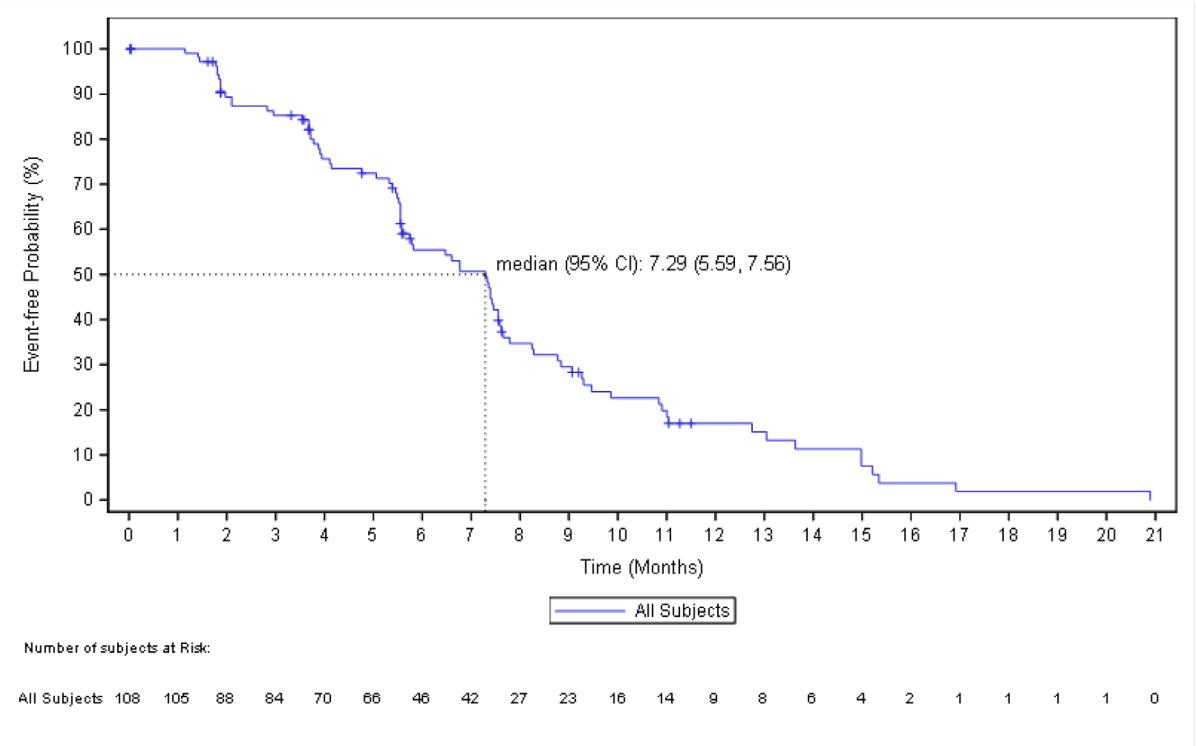
Secondary Endpoint: Disease Control Rate: The secondary endpoints of DCR assessed by BICR and by the investigator were identical. DCR assessed by BICR and by the investigator was 84.3% (95% CI: 76.0, 90.6) (Table OE 2).

Secondary Endpoint: Progression-Free Survival: For the secondary endpoint of PFS assessed by BICR, an event of disease progression or death occurred in 75.0% of subjects (25.0% of subjects censored) (CBGJ398X2204 Primary CSR Table 14.2.8.1) and the median PFS was 7.29 months (95% CI: 5.59, 7.56) (Figure OE 4).

The secondary endpoint of PFS assessed by the investigator was similar to PFS assessed by BICR. PFS, an event of disease progression assessed by the investigator or death, occurred in 81.5% of subjects (18.5% of subjects censored) (CBGJ398X2204 Primary CSR Table 14.2.8.2) and the median PFS was 6.74 months (95% CI: 5.55, 7.56) (CBGJ398X2204 Primary CSR Figure 14.2.9.2).

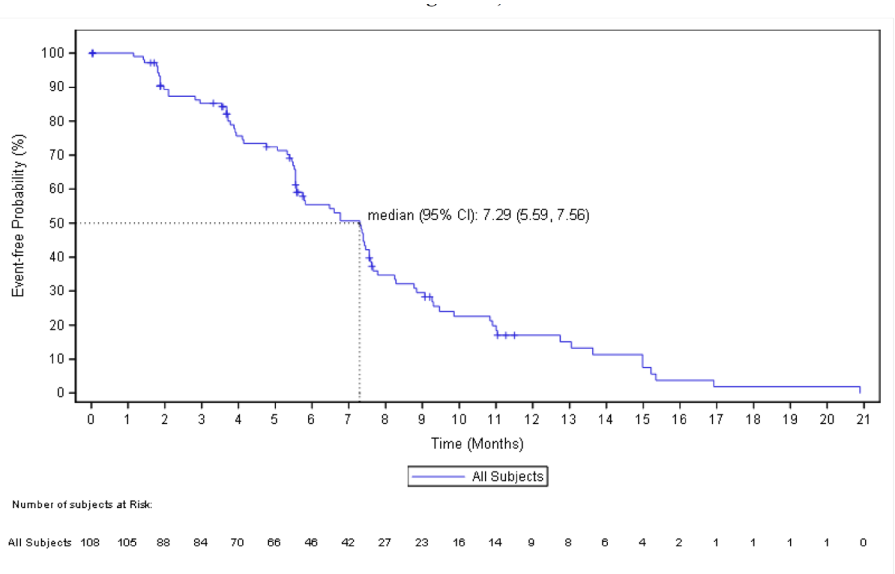
Secondary Endpoint: Overall Survival: For the secondary endpoint of OS, an event of death occurred in 82.4% of subjects (CBGJ398X2204 Primary CSR Table 18). The median OS was 11.86 months (Figure OE 5).

Figure OE 4: Kaplan-Meier Plot of Progression-free Survival by BICR (Cohort 1 FAS With FGFR2 Fusion/Rearrangement)



BICR=blinded independent central review; CI=confidence interval.
Data cutoff date: 01 March 2021.
Source: CBGJ398X2204 Primary CSR Figure 4

Figure OE 5: Kaplan-Meier Plot of Overall Survival (Cohort 1 FAS With FGFR2 Fusion/Rearrangement)



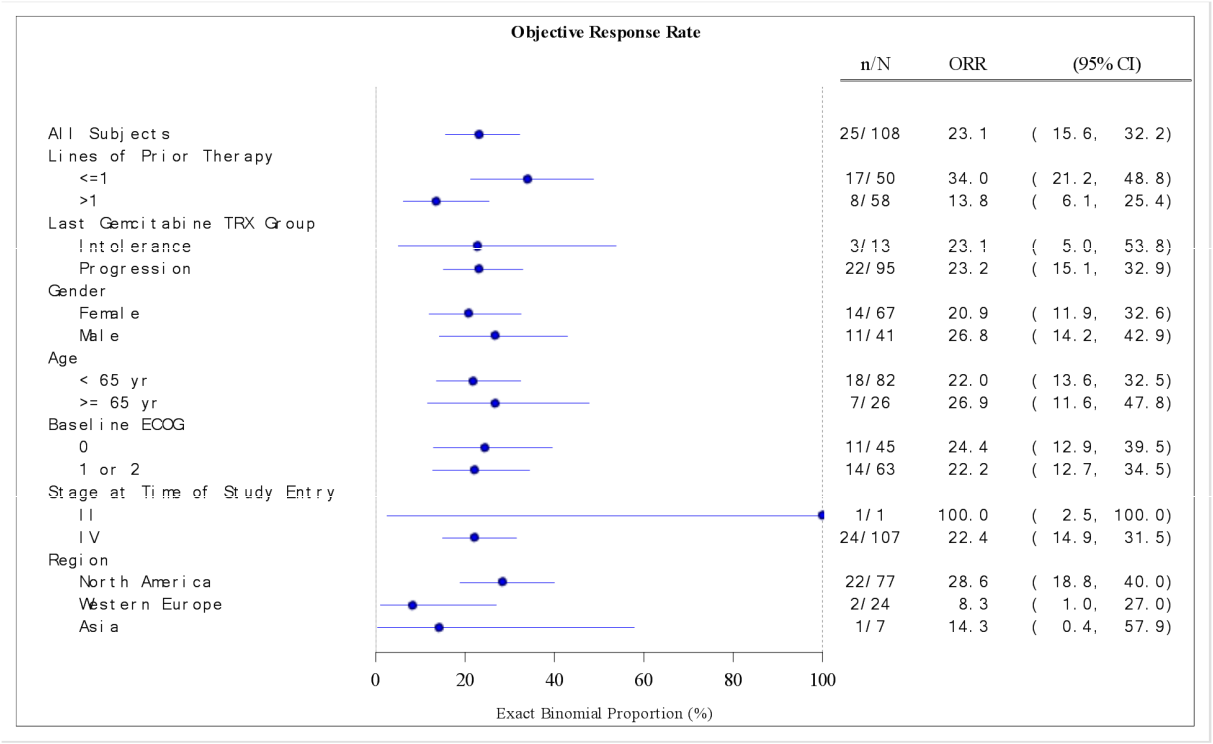
BICR=blinded independent central review; CI=confidence interval.
Data cutoff date: 01 March 2021.
Source: CBGJ398X2204 Primary CSR Figure 4

Ancillary analyses

Subgroup Analysis of Objective Response Rate by BICR

There were no differences between subgroups for ORR assessed by BICR (Figure OE 6) with regards to lines of prior therapy, sex, age, or region, as the 95% CIs overlapped in each subgroup. However, there were numerical differences (>2-fold) between subgroups, with ORR appearing higher in subjects with ≤1 prior line of therapy (ie, true second-line subjects) and in North America compared with Western Europe and Asia (although the sample size is small outside of North America). Numerical differences (>4-fold) in ORR for stage at time of study entry are most likely due to the small number of subjects (1 subject) in the Stage II group.

Figure OE 6: Subgroup Analyses of Objective Response Rate Assessed by BICR (Cohort 1 FAS With FGFR2 Fusion/Rearrangement)



BICR=blinded independent central review; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ORR=objective response rate; TRX=treatment; yr=year.
Data cutoff date: 01 March 2021.
Source: CBGJ398X2204 Primary CSR Figure 7

The results of additional subgroup analyses regarding the secondary endpoints please refer to the Clinical Part of these AR; in general they are consistent and not very additionally informative.

3.3.4.3. Summary of main efficacy results

Table OE3 Summary of efficacy for Study CBGJ398X2204

Title: A phase II multicenter, single arm study of oral BGJ398 in adult patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy	
Study identifier	CBGJ398X2204 EudraCT Number: 2013-005085-19 Clinical Trials Identifier: NCT02150967
Design	Prospective, non-randomised, single arm, open-label, multicentre clinical trial
Date first subject treated: **Date of data cutoff** for this Submission:	23 July 2014 01 March 2021

Hypothesis	N/A		
Treatments groups	Cohort 1 (FGFR2 rearrangements, N= 108) Cohort 2 (Other FGF/FGFR alterations, planned ~30, N= NR) Cohort 3 (FGFR2 fusions (must receive prior treatment with an FGFR2 inhibitor), planned ~20, N= NR)		Treatment: 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. Duration of treatment: Study drug is being continued until disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, or death.
Endpoints and definitions	Primary endpoint: Overall Response Rate (cohort 1) assessed by blinded independent central review (BICR)	ORR (BICR)	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
	Secondary endpoint: Overall Response Rate (cohort 1) **assessed by investigator**	ORR (INV)	The primary endpoint for this study is overall response in Cohort 1 assessed according to investigators review (INV) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
	Secondary endpoint: progression free survival	PFS	First dose to progressive disease or death (all cohorts)
	Secondary endpoint: Best Overall Response	BOR	Best response across all time points up to progression
	Secondary endpoint: disease control rate by BICR and investigator	DCR	Complete response + partial response + stable disease (all cohorts)
	Secondary endpoint: overall survival	OS	First dose to death due to any cause (all cohorts)
Results and Analysis			
Analysis description	Primary Analysis		

Analysis population and time point description	Analysis population: The Full Analysis Set (FAS) was used for the primary analysis. The FAS included all subjects in Cohort 1 who had received ≥1 dose of infigratinib. ITT / Per-Protocol Set ?		
Descriptive statistics and estimate variability		**Assessment of Disease by**	
		BICR	**Investigator**
	Primary Endpoint, n	108	NA
	Objective Response rate[a] n(%)	25 (23.1)	
	(95%CI)[b]	(15.6, 32,2)	
	Secondary Endpoint, n	NA	108
	Objective Response rate[a] n(%)		35 (32.4)
	(95%CI)[b]		(23.7, 42.1)
	Duration of response c, n Kaplan-Meier estimate	25	35
	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)
	Response onset, n	25	35
	Mean (SD), 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
	Confirmed CR, n (%)	1 (0.9)	0
	Confirmed PR, n (%)	24 (22.2)	35 (32.4)
	Stable disease d, n (%)	66 (61.1)	56 (51.9)
	Unconfirmed CR/PR, n (%)	14 (13.0) e	10 (9.3)
	Progressive disease, n (%)	11 (10.2)	11 (10.2)
	Not done, n (%)	6 (5.6)	6 (5.6)
	Disease control rate f, n	108	108
	Event, n (%)	91 (84.3)	91 (84.3)
	(95% CI) b	(76.0, 90.6)	(76.0, 90.6)
	Progression-free survival g, n	108	108
	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, n	108	
	Death event, n (%)	89 (82.4)	
	Median (95% CI) b, months	11.86 (10.68, 14.85)	
	BICR=blinded independent central review; CI=confidence interval; CR=complete response; max=maximum; min=minimum; NA=not applicable; PR=partial response; SD=standard deviation. + indicates numbers reported for subjects whose response is still ongoing. a Proportion with a best overall response of confirmed CR or PR. b Binomial proportion with exact 95% CI. c uration of response calculated as months from initial response to disease progression or death due to any cause in confirmed responders. d Non-CR/nonprogressive disease considered stable disease for subjects who only have non-target lesions at baseline. e All 14 subjects with unconfirmed response discontinued the study as of the data cutoff of 01 March 2021. Of these 14 subjects, 9 subjects discontinued for disease progression per investigator's assessment, 4 subjects discontinued for adverse events, and 1 subject discontinued for physician decision. f Subjects with best overall response as confirmed CR, PR, or stable disease (including unconfirmed CR/PR). g 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. Data cutoff date: 01 March 2021. Source: CBGJ398X2204 Primary CSR Table 15		

3.3.4.4. Clinical studies in special populations

Not provided.

3.3.4.5. In vitro biomarker test for patient selection for efficacy

Patient enrolment in the clinical study CBGJ398X2204 was based on determination of FGFR2 gene fusion or rearrangement. In study report CBGJ398X2204 it has been indicated that different methods by various local laboratories have been employed to analyse FGFR2 gene alteration in tumour tissue samples. Methods employed comprise RNA/DNA based next generation sequencing, FISH, and qPCR. Detailed information on the analytical performance (including assay platform, specimen, pre-analytical sample processing requirements and read-out) and validity of assays has not been indicated and should be provided. As regards analytical validity, the suitability of assays used should be demonstrated (e.g. robustness, accuracy, specificity, sensitivity and linearity, as appropriate for method). The testing laboratories involved should be identified and their accreditation status should be indicated. It should be

clarified if round robin tests were performed at local labs to demonstrate compliance with suitable clinical laboratory quality standards.

The analytical and/or clinical cut-off value selection as a basis for decision of patient enrolment should be stated and discussed for each method. Clinical validity of the methods (sensitivity/specificity) should be demonstrated. Further, it is indicated that results from local labs should have been verified by re-analysis of samples by the central lab (foundation one assay). This should be further elaborated, data for concordance testing should be summarised and the level of agreement of methods used at local labs with the central lab should be indicated. It should be indicated if tumour heterogeneity is relevant in case of cholangiocarcinoma with FGFR2 fusion or rearrangement and if/how this has been addressed during analytical assay validation.

The proposed product labelling indicates that the presence of an FGFR2 fusion or rearrangement is to be determined by an experienced laboratory using a validated test method prior to initiation of treatment with infigratinib. This is in contrast with the current PI, stating in chapter 4.2 that "an appropriate test" should be used. ("Assessment for FGFR 2 fusion positivity in tumour specimen should be performed with an appropriate diagnostic test."). The PI should be amended accordingly.

3.3.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

3.3.4.7. Supportive study(ies)

N/A

3.3.5. Discussion on clinical efficacy

The applicant has submitted an application for a conditional marketing authorization (CMA) based on the results of Cohort 1 in the single-arm phase 2 study CBGJ398X22204 in the second-line treatment setting and beyond of locally advanced or metastatic cholangiocarcinoma (CCA) with FGFR2 fusion or rearrangement. CCA is quite rare, with 1 to 2 patients per 100,000 in the EU and the US. The 5-year survival rate is reported to be low and varies by stage: 50% for stage I, 30% for stage II, 10% for stage III, and 0% for stage IV (Valle et al 2017). Patients with FGFR2 rearrangement or fusion are reported to have a better prognosis that patients without FGFR genetic alteration (Churi et al, 2014; Jain et al, 2018).

For this indication Pemigatinib is currently approved in the EU based on an OOR of 37.0% including 4 subjects who reached durable CR and a median duration of response of 8.08 months (actual SmPC of Pemazyre®).

Design and conduct of clinical studies

Efficacy data for infigratinib in the applied target population of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement is based on primary analysis results of Study CBGJ398X2204 from subjects who received ≥1 dose of infigratinib (Cohort 1 FAS With FGFR2 Fusion/Rearrangement).

The applicant conducted a SAT against scientific advice from EMA, which clearly stated, that the most robust evidence could come from a direct comparison with a limited choice of best investigator's options in true 2nd line to limit heterogeneity. The lack of comparator is a clear disadvantage in the MAA.

The inclusion/exclusion criteria for Cohort 1 of the study CBGJ398X22204 as presented after several changes due to interim-analyses triggered amendments reflect an advanced CCA target population as

currently applied. Baseline characteristics were generally similar between the population of the study CBGJ398X22204 and the population observed with FGFR genetic aberrations (GAs) by the experts in the field (Jain et al, 2018). Insofar, it is agreed that the included population reflects adequately the intended target population.

Patient enrolment in the clinical study CBGJ398X2204 was based on determination of FGFR2 gene fusion or rearrangement. In study report CBGJ398X2204 it has been reported that different methods by various local laboratories have been employed to analyse FGFR2 gene alteration in tumour tissue samples. Methods employed comprise RNA/DNA based next generation sequencing, FISH, and qPCR. However, no details were submitted for assessment of validity of the methods used, which is deemed essential to conclude about diagnostic reliability with respect to the included population in the trial. Also information on the types of FGFR2 mutations identified at the time of inclusion according local and/or central assessment was not found and should be submitted. Time since diagnosis as well as the impact of surgery in patients before inclusion in the trial should also become transparent and be correlated with the outcome (responder/non-responder). Moreover, the pharmaceutical FMI used in the subject who reached response according to CR and PR should become evaluable.

The primary endpoint of the study CBGJ398X22204 is defined as the ORR assessed by BICR in participants of the Cohort 1 with FGFR2 rearrangements or fusions. ORR assessed by BICR is considered acceptable to investigate an antitumour activity of a medicinal product in patients with a defined tumour type, nevertheless in the context of a single-arm trial in which the magnitude of response rate is unknown to be predictive of a clinical benefit, it could be difficult to decide whether assess if the effect observed is clinically relevant and not only related to the favorable prognosis of patients with FGFR2 genetic alterations. ORR is supported by Best Overall Response (BOR), duration of response (DOR) PFS and OS as secondary endpoints all assessed by BICR. In addition, investigator's assessment regarding the outcome for the same endpoints was submitted. However, since investigator's assessment in general in clinical trials is considered to be more biased and mostly more positive than an independent blinded assessment, the relevance of investigator's assessment of efficacy is minor.

Participants were assigned to cohorts 1, 2 and 3 based on tumour FGF/FGFR status in this explorative trial. Cohort 1 included participants with FGFR2 mutations only. It is acknowledged that with increased understanding of FGFR2 genetic alterations in CCA, the terminology has evolved to "rearrangements or fusions" to more precisely describe these genetic alterations which is reflected in the claimed indication. However, details of the underlying mutations and the methods used for determination in cohort 1 remain not evaluable at present and information need to be provided. A large heterogeneity in the included trial population with respect to pre-treatment in previous line is noted, but the impact of the differences on the outcome is currently not adequately available and needs further clarification. Whether the applicant's claim that the target population in trial CBGJ398X22204 was in a more advanced disease stage and more intensively pretreated than in the pivotal FIGHT-202 SAT trial for pemigatinib and that this factor explains the significantly inferior outcome alone is difficult to assess, however may be challenged and needs further evaluation. Similarly, it needs to be considered that the trial was started in "patients who failed or are intolerant to platinum-based chemotherapy". From the submitted information the number of subjects never received platinum-based chemotherapy could not be clearly evaluated.

Moreover, this issue indicates the difficulties in evaluating data from multiply analysed, fundamentally amended, uncontrolled, open-label study. In general all analyses of this study need to be considered exploratory and results efficacy is claimed are based on post-hoc selection of subpopulations, which are hardly acceptable in the Rapporteur's view. Generally, it cannot be assumed that observed ORR or DoR in this SAT are unbiased estimates. Subtle selection mechanisms that are associated with prognosis can have impact at the point of recruiting patients – both due to investigator decision making as well as patient's choices. As well known, such SATs are consequently particularly sensitive to selection bias. Additionally, the impact of treatment on PFS and OS cannot be disentangled from prognostic factors in

SATs, which is particularly relevant in this context where it is not clear yet whether FGFR2 fusions/rearrangement is a positive prognostic factor**.**

Of note, the applicant did also not make an attempt to contextualise the results, e.g. by comparing to external data, although some approaches for contextualisation were discussed during CHMP scientific advice. A retrospective, observational, natural history study investigating the OS of patients with cholangiocarcinoma with FGFR2 gene fusions/rearrangements and those with FGFR2 WT using RWD from Flatiron Health and Foundation Medicine was conducted but not directly used for contextualisation. Considering the limitations of external comparisons, especially when not being pre-specified prior to SAT conduction, it is acknowledged that such comparisons would not add much evidence. Still, in the context of a conditional marketing authorisation with another product conditionally authorised for the same indication, demonstration that infigratinib fulfils the unmet medical needs to a similar or greater extent than what is understood for the already conditionally authorised product is required such that contextualisation is needed.

In a SAT, in accordance with the ITT principle, the analysis should usually include all enrolled patients (i.e. patients who provided informed consent) and not only treated patients. It should be clarified whether enrolled patients were not treated and an analysis considering these as non-responders should be provided.

The decision to restrict the enrolment and analysis primarily to patients with FGFR2 fusion/rearrangement was made by protocol amendments while the study was ongoing based on interim data suggesting that this subgroup of patients were more likely to respond to therapy with infigratinib, which may lead to biased estimates. Therefore, during CHMP scientific advice, it was recommended to restrict the analysis to patients included only after such changes, which was not followed for primary analysis but a sensitivity analysis was conducted including only patients after protocol amendment 2 introducing the restriction to FGFR2 fusion/rearrangement.

Hypothesis testing was neither pre-specified nor performed but only descriptive analyses were provided. The sample size was justified based on the achievable precision of estimation (in terms of the width of the 95% confidence interval for ORR). This is agreed for an uncontrolled study, as any threshold for ORR for deciding on study success needs to be considered arbitrary when it cannot be anchored based on clinical reasoning.

Moreover, interpretation of efficacy (as well as safety) is hampered by the fact that pharmaceutical development in this trial was premature. During the trial subjects were treated with 4 different formulations and -as detailed in the PK part of this AR- significant variation in bioavailability of the administered formulation are obvious and may have had a relevant impact on the efficacy (and safety) observed. Since formulation IV, the currently applied marketing formulation, was obviously only used very late in Cohort 1 and bioequivalence to the previous formulation is challenged, it remains unknown whether the submitted data adequately regarding the benefits and risk of the proposed posology. In fact, it remains unknown, whether results regarding safety and efficacy with the now applied infigratinib marketing formulation are comparable to those here assessed**.**

Treatment in the trial was recommended with infigratinib tablets at a dose of 125 mg (one 100 mg capsule and one 25 mg capsule), taken once daily for 21 days followed by 7 days off therapy. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. However, the presented data indicate that only a small proportion of subjects could be treated with the applied 125 mg dose as proposed in the posology It seems that most subjects need toxicity-driven sustainable dose reductions shortly after start of treatment and were not able to return to the 125 mg dose; thus, the applied posology in general seems pre-mature, not sufficiently justified and hardly tolerable in the target population and thereby is likely to have contributed to the overall low efficacy.

In addition, it seems that even the rules for dose reductions as listed in the SmPC were not pre-specified in the protocol and reliability of these recommendations may be challenged.

Efficacy data and additional analyses

The median duration of exposure to infigratinib was 5.59 months (range: 0.03 to 39.10 months). Duration of exposure was ≤6 months for 51.9% of subjects, between 6 and ≤12 months for 35.2% of subjects, and >12 months for 13.0% of subjects. However, only one patient was still on treatment at time data cut-off; this may in principle reflect the advanced CCA stage, a low tolerability and/or an overall low efficacy. Nevertheless, it also means that data presented is mature for assessment and no relevant additional information can be probably expected from further follow up of this trial, which is offered as part of the commitment to fulfil the condition.

Efficacy results for in the pivotal Cohort 1 in trial CBGJ398X22204 provide some evidence for efficacy as assessed by blinded independent central review (BICR) in the included population. The primary endpoint [ORR was 23.1% (95% confidence interval [CI]: 15.6, 32.2) However, due to the data-driven design changes of the study design, the true coverage probability of the calculated confidence interval for ORR may also be smaller than 95% and thus clearly not overwhelming enough to allow approval based on SAT data in the Rapporteur's view.

In the total population of 108 patients, best-overall-response (BOR) in the BICR assessment is reported as 1 (0.9%) subject with a confirmed CR, 24 subjects (22.2%) had confirmed PR information, while 66 subjects (61.1%) were assessed to have stable disease according BICR-assessment. The BOR outcome in the remaining subjects (15.8%) was reported as "unconfirmed" and progressive disease or "not done", which seems rather confusing. Moreover, information regarding the patient who reached CR is not sufficiently comprehensible; more details and sufficiently detailed to allow confirmation of this outcome at present. More clarification on the impact of pre-treatment and potentially surgery is needed.

The K-M estimate for median duration of response (DOR) assessed by BICR is reported with 5.55 months (95% CI: 3.78, 7.66), with the longest duration of 19.12 months. Nine subjects (36.0%) had DOR ≥6 months, 4 subjects (16.0%) had DOR ≥9 months, and 1 subject (4.0%) had DOR ≥12 months. In order to further assess the differences in duration of response the applicant is requested to provide more details regarding baseline data in these patients, particularly with respect to the time since diagnosis and the treatment intensity (time patient was treated without dose reductions as well as time of off-treatment).

Disease progression assessed by BICR or death occurred in 75.0% of subjects with a median PFS of 7.3 months (95% CI: 5.59, 7.56); 82.4% of the included subjects died until data-cut-off. Median OS is calculated with 11.86 months (95% CI: 10.68, 14.85). More details are requested with respect to the disease duration before inclusion in then trial and overall survival for responder and non-responder,

No meaningful additional information is derived from the response assessment performed by the investigators, which was in general slightly more favourable compared with that performed by the BICR, however probably more likely to be biased.

In addition, for time to event endpoints (DOR, PFS, OS), the numbers of censored patients should be provided by censoring reason. If a relevant number of patients were censored for other reasons than being event-free at analysis cut-off, relevant bias due to informative censoring cannot be excluded. Sensitivity analyses should be provided in this case (including worst-case analyses). In the analyses conducted by the applicant, events of disease progression endpoints are ignored when observed after two or more missed visits, and the data are censored at the last adequate tumour assessment before the missing assessment. This approach is not in line with PFS endpoint definition as per Appendix 1 to the EMA guideline on the evaluation of anticancer medicinal products in man. The applicant should

justify the current approach in light of the observed data (e.g. when PFS was not observed but death was observed) and provide sensitivity analyses where events are analysed as observed regardless of missed scheduled assessments.

The applicant should also clarify the estimand targeted with the current analysis strategy. There are cases where subjects' time-to-progression are censored due to a competing (intercurrent) event, such as treatment discontinuation due to an adverse event, and the resulting time-to-progressoin dataset is analysed using K-M method. Are the respective time-to-progression curves supposed to represent hypothetical scenarios as if the competing intercurrent event did not occur or actual time-to-progression distribution regardless of intercurrent event occurrence?

Also overall survival for responders vs non-responders should be provided for the primary analysis population (although it is acknowledged that this analysis needs to be interpreted with care because of immortal time bias, i.e. patients need to survive for some time to achieve a response such that a possible longer survival of responders is not necessarily causally explained by response).

Since other contextualisation in the FGFR2 subtype of CCA is not possible, a comparison with the approved FGFR2 inhibitor pemigatinib seems indicated.

Pemigatinib has shown in a similarly sized population of 107 subjects with FGFR2 rearrangement or fusion enrolled in Cohort A of the pivotal FIGHT-202 trial, a significantly higher ORR of 37.0% [(95% CI: 27.94, 46.86) versus 23.1% in Infigratinib. What ever the reasons were, treatment outcome was also consistently superior; 4 subjects had a clinical important confirmed and durable CR (versus 1 in infigratinib) and 36 subjects had a confirmed PR (Infigratinib: 24 PR). 46.7% were assessed as SD as a best response; disease control rate was 82.2%. Similarly, among the 40 participants with IRC-assessed confirmed tumour responses, median DOR was about two and half months longer [Pemigatinib: 8.08 months (95% CI: 5.65, 13.14) versus Infigratinib: 5.55 months (95% CI: 3.78, 7.66)]. Even acknowledging the intrinsic difficulties from inter-trial comparisons the outcome of pemigatinib may be assessed as clearly superior according to the data available and published to the scientific community.

Considering that a CMA needs confirmation by an additional comparative trial, the described superiority of outcome for pemigatinib may affect the feasibility of the confirmative trial as proposed by the applicant for the first line. It seems questionable, whether patients will give their consent to be included in a clinical trial with a product showing an inferior outcome as infigratinib in the preliminary data available.

Additional expert consultation

Not at present.

Assessment of paediatric data on clinical efficacy

N/A

Additional efficacy data needed in the context of a conditional MA

The applicant has proposed to provide confirmatory data from a phase 3 RCT Study QBGJ398-301 (PROOF Trial) with gemcitabine plus cisplatin in the control arm in the first-line setting of previously untreated cholangiocarcinoma patients with FGFR2 fusions/rearrangements. The applicant stated that the first patient was included on 27 Dec 2019 and analysis for the primary outcome is expected for 2027. However, no information regarding the overall recruitment during the last 2 years was given.

3.3.6. Conclusions on clinical efficacy

Efficacy claims for infigratinib monotherapy in the treatment of "adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement" are based on a single pivotal study CBGJ398X22204.

a) All analyses of this study need to be considered exploratory as the efficacy results claimed are based on post-hoc selection of subpopulations from a single multiply analysed, fundamentally amended, uncontrolled, open-label study.

b) The size of the effects on ORR 23.1% (95% CI 15.6, 32.2) and median DOR 5.55 months (95% CI 0.92, 19.12) is not such that it is reasonable to assume clinically relevant effects on PFS, OS or HRQoL and exclude a major detriment in any of these effects.

a) In the absence of a randomised comparator the impact of the treatment with infigratinib on PFS and OS cannot be reliably estimated. In particular, the impact on PFS and OS cannot be disentangled from prognostic factors, which is particularly relevant in this context where it is not clear yet whether FGFR2 fusions/rearrangement is a positive prognostic factor.

Therefore, data are not considered sufficient to conclude on a clinical benefit in the applied indication.

3.3.7. Clinical safety

The clinical development programme contributing to the safety analysis for this marketing application comprises 19 clinical studies, with 844 subjects exposed to infigratinib.

Safety assessment in this application was performed based on analysis and discussion of key safety data mainly in the population of subjects with an FGFR2 gene fusion or rearrangement in CBGJ398X2204 Cohort 1, who received at least 1 dose of study drug by the analysis cut-off date of 01 March 2021 and supporting evidence from integrated analyses across the clinical development programme.

The key datasets for safety evaluation in this summary of safety are (1) the primary safety analysis set in the applied target population and (2) the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set.

- The **primary safety analysis set** consists of **108 subjects with an FGFR2 gene fusion or rearrangement in CBGJ398X2204 Cohort 1** who received at least 1 dose of study drug by the analysis **cut-off date of 01 March 2021**; all subjects received infigratinib monotherapy on the 125 mg 3 weeks on/1 week off schedule. Analyses were conducted per the CBGJ398X2204 SAP and the CBGJ398X2204 Supplementary SAP, and most outputs based on this analysis set are included in the CBGJ398X2204 Primary CSR. This analysis set is referred to as Interim Analysis Set 2 for Cohort 1 in the CBGJ398X2204 Primary CSR.
- The **"125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set"** consists of **363 subjects who received infigratinib 125 mg QD on a 3 weeks on and 1 week off dosing schedule** and received at least 1 dose of 125 mg infigratinib who enrolled into clinical studies **CBGJ398X2101 (115 subjects with advanced solid malignancies), CBGJ398X2201 (26 subjects with glioblastoma), CBGJ398X2204 (Cohorts 1-3 108+30), and CBGJ398XUS04 (84 subjects with advanced solid or haematological malignancies) and** (ISS Table 14.1.1.1).

  Subjects were summarised according to the initially received formulation (CSF, FMI I, FMI III, or FMI IV), regardless of whether a subject switched formulation during the treatment period. A majority of the ISS outputs are based on this analysis set.

The **programme-wide safety analysis set** consists of **809 subjects** who received at least one dose of infigratinib in all sponsor-initiated clinical studies

Non-clinical toxicology studies in rats and dogs have identified bone as main target organ. After 26 or 39 weeks of infigratinib administration the important toxicities observed are changes in calciumphosphorus homeostasis and secondary effects including ectopic tissue mineralisation in multiple tissues and in large and small blood vessels as well as changes in the cornea. Similarly, pharmacologically related changes occurred in bone, epithelial tissues, teeth, and/or hair/skin.

Target organ toxicities only observed in 2-week repeat-dose toxicity studies included the hematopoietic system in rats, and the liver, gallbladder, and bone marrow in dogs. According to the provided information these infigratinib-related target organ toxicities were at least partially reversible with the exception of incisor teeth and hair coat changes, and ectopic tissue mineralisation at some dose levels/dosing durations. Moreover, infigratinib was also associated with the potential for embryo-fetal toxicity. These toxic effects are probably all caused by the pharmacological activity of infigratinib (ie, inhibition of FGFR1-3) and were in general also observed in pemigatinib, a similar tyrosine kinase inhibitor of FGFRs 1-3 marketed in the EU since March 2021 for a comparable indication.

3.3.7.1. Patient exposure

In the primary safety analysis set subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS had a median exposure of 5.59 months, and the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set had a median exposure of 2.79 months. In, median duration of exposure to infigratinib was 5.59 months (range: 0.03-39.10 months) (OS1). Slightly more than half of the subjects were exposed to infigratinib for ≤6 months (56/108, 51.9%). 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%.

It seems important to note that exposure in the 125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set was very low (< 3 cycles in median), which challenges the reliability of this safety data in general.

Table OS-1: Exposure to Infigratinib (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set					**Primary Safety Analysis Set**
	Formulation					
	CSF	**FMI I**	**FMI III**	**FMI IV**	**All Subjects**	**All Subjects**
	(N = 129)	**(N = 157)**	**(N = 51)**	**(N = 25)**	**(N = 363)**	**(N = 108)**
Duration of treatment (months)						
Mean (SD)	3.68 (7.11)	5.03 (4.82)	7.88 (7.25)	3.12 (2.55)	4.85 (6.16)	**6.79 (5.44)**
Median	1.61	3.45	6.31	2.33	2.79	**5.59**
Min, max	0.13, 62.00	0.03, 31.05	0.23, 39.10	0.62, 11.73	0.03, 62.00	**0.03, 39.10**
≤2 months	84 (65.1)	55 (35.0)	10 (19.6)	11 (44.0)	160 (44.0)	**18 (16.7)**
>2 to ≤4 months	23 (17.8)	32 (20.4)	8 (15.7)	8 (32.0)	71 (19.6)	**21 (19.4)**
>4 to ≤6 months	7 (5.4)	21 (13.4)	6 (11.8)	3 (12.0)	37 (10.2)	**17 (15.7)**
>6 to ≤8 months	4 (3.1)	18 (11.5)	8 (15.7)	1 (4.0)	31 (8.5)	**18 (16.7)**
>8 to ≤10 months	1 (0.8)	8 (5.1)	6 (11.8)	1 (4.0)	16 (4.4)	**10 (9.3)**
>10 to ≤12 months	0	7 (4.5)	3 (5.9)	1 (4.0)	11 (3.0)	**10 (9.3)**
>12 months	10 (7.8)	16 (10.2)	10 (19.6)	0	37 (10.2)	**14 (13.0)**

Table OS-1: Exposure to Infigratinib (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)						
	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set					Primary Safety Analysis Set
	Formulation					
	CSF	FMI I	FMI III	FMI IV	All Subjects	All Subjects
	(N = 129)	(N = 157)	(N = 51)	(N = 25)	(N = 363)	(N = 108)
Cumulative actual dose (mg)						
Mean	8588.9	10812.9	16248.0	8219.0	10643.8	**14353.7**
(SD)	(11113.29)	(9502.28)	(12854.77)	(6566.61)	(10728.69)	**(10196.59)**
Median	4875.0	8625.0	13125.0	6000.0	7425.0	**12337.5**
Min, max	500, 69045	125, 55850	875, 63750	1200, 29075	125, 69045	**125, 63750**
Relative dose intensity (%)a						
Mean (SD)	93.6 (20.77)	80.8	76.4	86.7 (17.03)	85.1	**77.6 (17.71)**
Median	100.0	82.9	74.2	85.2	87.5	**77.6**
Min, max	34, 133	31, 105	42, 103	26, 105	26, 133	**38, 105**
≤50%	5 (3.9)	8 (5.1)	3 (5.9)	1 (4.0)	17 (4.7)	**5 (4.6)**
>50 to ≤75%	18 (14.0)	49 (31.2)	24 (47.1)	3 (12.0)	95 (26.2)	**45 (41.7)**
>75 to ≤90%	22 (17.1)	39 (24.8)	7 (13.7)	10 (40.0)	78 (21.5)	**23 (21.3)**
>90 to ≤100%	47 (36.4)	51 (32.5)	16 (31.4)	8 (32.0)	122 (33.6)	**29 (26.9)**
>100%	37 (28.7)	10 (6.4)	1 (2.0)	3 (12.0)	51 (14.0)	**6 (5.6)**
max=maximum; min=minimum; SD=standard deviation. Relative dose intensity = actual cumulative dose (mg) / planned cumulative dose (mg) within the actual treatment duration. Source: ISS Table 14.3.0.1.1; CBGJ398X2204 Primary CSR Table 14.3.0.1.1						

3.3.7.2. Adverse events

In the pivotal trial CBGJ398X2204 overall, 107 subjects (99.1%) in subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS had at least 1 AE and 104 subjects (96.3%) had at least 1 treatment-related AE. (Table OS2)

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 and thirty-five subjects (32.4%) had a treatment-emergent SAE, of whom 9 (8.3%) had an investigator-assessed treatment-related SAE. One subject (0.9%) had an AE with an outcome reported as fatal.

Twenty-one subjects (19.4%) 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).

Seventy-one subjects (65.7%) had dose interruption due to an AE; 66 subjects (61.1%) had dose adjustment due to an AE. Most subjects (95.4%) had an AE that required concomitant medication or non-drug therapy.

Table OS 2: Overall Summary of Adverse Events (Subjects with FGFR2 Fusion/ Rearrangement in Cohort 1 FAS)		
Safety event	**Subjects with FGFR2 Fusion/Rearrangement in Cohort 1 FAS (N=108) n (%)**	**125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set Formulation All Subjects (N = 363)**
Any AE	107 (99.1)	360 (99.2)
Grade 3 or 4 AE	71 (65.7)	233 (64.2)
AE outcome fatal	1 (0.9)	NR
Serious AE (SAE)	35 (32.4)	133 (36.6)
Treatment-related AE	104 (96.3)	343 (94.5)
Serious treatment-related AE	9 (8.3)	26 (7.2)
AE leading to treatment discontinuation	21 (19.4)	55 (15.2)
AE leading to dose interruption	71 (65.7)	259 (71.3)
AE leading to dose adjustment	66 (61.1)	342 (94.2)
AE requiring concomitant medication or non- drug therapy	103 (95.4)	360 (99.2)
Abbreviations: AE=adverse event; FAS=Full Analysis Set; FGFR2=fibroblast growth factor receptor 2; SAE=serious adverse event. NR=not reported Source: Table 14.3.1.1.1		

Common adverse events:

The highest incidences of AEs for the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set were observed in the following SOCs: Gastrointestinal Disorders (84.0%), Metabolism and Nutrition Disorders (82.4%), General Disorders and Administration Site Conditions (68.6%), Investigations (58.4%), and Skin and Subcutaneous Tissue Disorders (57.6%). (Table OS3)

Table OS3: Most Frequent AEs (⩾10.0%) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)		
	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set Formulation	**Analysis Primary Safety Set**
	All Subjects	**All Subjects**
	(N = 363)	**(N = 108)**
Any AE, n (%)	360 (99.2)	107 (99.1)
Hyperphosphataemia	233 (64.2)	83 (76.9)
Fatigue	160 (44.1)	44 (40.7)
Stomatitis	140 (38.6)	59 (54.6)
Constipation	130 (35.8)	34 (31.5)
Alopecia	106 (29.2)	43 (39.8)
Decreased appetite	100 (27.5)	26 (24.1)
Blood creatinine increased	95 (26.2)	27 (25.0)
Diarrhoea	94 (25.9)	27 (25.0)
Nausea	94 (25.9)	21 (19.4)

Table OS3: Most Frequent AEs (⩾10.0%) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)		
	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set Formulation	**Analysis Primary Safety Set**
	All Subjects	**All Subjects**
	(N = 363)	**(N = 108)**
Dry mouth	92 (25.3)	28 (25.9)
Dry eye	88 (24.2)	39 (36.1)
Dysgeusia	82 (22.6)	34 (31.5)
Vomiting	78 (21.5)	25 (23.1)
Anaemia	71 (19.6)	20 (18.5)
Arthralgia	66 (18.2)	35 (32.4)
PPES	62 (17.1)	37 (34.3)
Hypophosphataemia	59 (16.3)	25 (23.1)
Abdominal pain	56 (15.4)	18 (16.7)
AST increased	55 (15.2)	25 (23.1)
Dry skin	55 (15.2)	26 (24.1)
Hypercalcaemia	55 (15.2)	29 (26.9)
Dyspepsia	51 (14.0)	19 (17.6)
Nail disorder	48 (13.2)	17 (15.7)
Weight decreased	48 (13.2)	17 (15.7)
Pain in extremity	46 (12.7)	17 (15.7)
Dyspnoea	43 (11.8)	10 (9.3)
Epistaxis	43 (11.8)	19 (17.6)
Back pain	42 (11.6)	16 (14.8)
Hyponatraemia	42 (11.6)	14 (13.0)
ALT increased	41 (11.3)	18 (16.7)
Cough	41 (11.3)	14 (13.0)
Headache	41 (11.3)	19 (17.6)
Vision blurred	41 (11.3)	23 (21.3)
Blood ALP increased	40 (11.0)	17 (15.7)
Lipase increased	40 (11.0)	13 (12.0)
Pyrexia	40 (11.0)	17 (15.7)
Urinary tract infection	39 (10.7)	10 (9.3)
Myalgia	38 (10.5)	14 (13.0)
Mucosal inflammation	37 (10.2)	1 (0.9)
Nail discolouration	37 (10.2)	20 (18.5)

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; PPES=palmar-plantar erythrodysaesthesia syndrome.
AEs reported for ⩾10.0% of all subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set are included in this table, sorted in descending order of frequency and then alphabetically for like frequenc.
Source: ISS Table 14.3.1.6.1.1; CBGJ398X2204 Primary CSR Table 14.3.1.3.1

Severity of Treatment-Emergent Adverse Events

For subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS, a total of 8 subjects (7.4%) had at least 1 AE with a maximum severity of Grade 1, 28 subjects (25.9%) had at least 1 Grade 2 AE, 61 subjects (56.5%) had at least 1 Grade 3 AE, and 10 subjects (9.3%) had at least 1 Grade 4 AE.

Seventy-one subjects (64.2%) had at least 1 AE with a maximum severity of Grade 3 or Grade 4, most were due to abnormal laboratory findings.

Grade 3 or Grade 4 AEs that occurred in ≥5% of all subjects included stomatitis (14.8%), hyponatraemia (13.0%), hypophosphataemia (13.0%), hyperphosphataemia (11.1%), increased lipase (7.4%), palmar-plantar erythrodysesthesia syndrome (6.5%), and hypercalcaemia (5.6%) (Table OS-4).

Grade 4 AEs included sepsis (3 subjects [2.8%], increased lipase (2 subjects [1.9%], stress fracture, increased amylase, increased gamma-glutamyltransferase, hypercalcaemia, hypophosphataemia, hyperbilirubinaemia and cataract (1 subject [0.9%] each).

Grade 4 AEs that were classified as serious were sepsis in 2 subjects and each one subject with stress fracture and hypercalcaemia.

The following table OS-4 provides an overview regarding the most frequent Grade 3 or 4 AEs in the relevant safety populations:

Table OS-4: Most Frequent Grade 3 or 4 AEs (⩾1.0%) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis	**Primary Safety Analysis Set**
	All Subjects	**All Subjects**
	(N = 363)	**(N = 108)**
Any Grade 3 or 4 AE, n (%)	233 (64.2)	**71 (65.7)**
Hypophosphataemia	34 (9.4)	**14 (13.0)**
Hyponatraemia	29 (8.0)	**14 (13.0)**
Hyperphosphataemia	28 (7.7)	**12 (11.1)**
Fatigue	25 (6.9)	**4 (3.7)**
Lipase increased	23 (6.3)	**8 (7.4)**
Stomatitis	22 (6.1)	**16 (14.8)**
PPES	15 (4.1)	**7 (6.5)**
Abdominal pain	13 (3.6)	**4 (3.7)**
Anaemia	13 (3.6)	**4 (3.7)**
Hypercalcaemia	13 (3.6)	**6 (5.6)**
Nausea	13 (3.6)	**1 (0.9)**
Sepsis	11 (3.0)	**4 (3.7)**
ALT increased	10 (2.8)	**2 (1.9)**
Decreased appetite	10 (2.8)	**1 (0.9)**
Vomiting	10 (2.8)	**1 (0.9)**
Dehydration	9 (2.5)	**2 (1.9)**
Diarrhoea	9 (2.5)	**3 (2.8)**
Dyspnoea	9 (2.5)	**0**
Pain in extremity	9 (2.5)	**2 (1.9)**
Urinary tract infection	8 (2.2)	**1 (0.9)**

Table OS-4: Most Frequent Grade 3 or 4 AEs (⩾1.0%) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)		
	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis	**Primary Safety Analysis Set**
	All Subjects	**All Subjects**
	(N = 363)	**(N = 108)**
AST increased	7 (1.9)	**3 (2.8)**
Back pain	7 (1.9)	**1 (0.9)**
Blood ALP increased	6 (1.7)	**4 (3.7)**
Mucosal inflammation	6 (1.7)	**1 (0.9)**
Cataract	5 (1.4)	**2 (1.9)**
GGT increased	5 (1.4)	**1 (0.9)**
General physical health	5 (1.4)	**1 (0.9)**
Deterioration		
Pyrexia	5 (1.4)	**1 (0.9)**
Acute kidney injury	4 (1.1)	**2 (1.9)**
Arthralgia	4 (1.1)	**0**
Asthenia	4 (1.1)	**0**
Blood bilirubin increased	4 (1.1)	**2 (1.9)**
Constipation	4 (1.1)	**1 (0.9)**
Haemoglobin decreased	4 (1.1)	**0**
Hyperbilirubinaemia	4 (1.1)	**2 (1.9)**
Hyperkalaemia	4 (1.1)	**2 (1.9)**
Hypocalcaemia	4 (1.1)	**0**
Hypoxia	4 (1.1)	**1 (0.9)**
Pneumonia	4 (1.1)	**1 (0.9)**
Syncope	4 (1.1)	**0**

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase; PPES=palmar-plantar erythrodysaesthesia syndrome. Grade 3 or 4 AEs reported for ⩾2.0% of all subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set are included in this table, sorted in descending order of frequency and then alphabetically for like frequency.

Source: ISS Table 14.3.1.6.4.1; CBGJ398X2204 Primary CSR Table 14.3.1.6.1

Grade 4 AEs reported for ≥2 subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set were sepsis (8 subjects [2.2%]), increased lipase (5 subjects [1.4%]), hypophosphataemia (4 subjects [1.1%]), septic shock (2 subjects [0.6%]), respiratory failure (2 subjects [0.6%]), and cataract (2 subjects [0.6%]) (ISS Table 14.3.1.2.1.1).

Related Adverse Events

Related AEs reported for ≥5.0% of all subjects in descending order of frequency for the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set are provided in Table OS-5. The most common related AEs (≥20.0%) as assessed by investigators in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set were generally on-target effects of infigratinib and included hyperphosphataemia, stomatitis, fatigue, alopecia, dry mouth, and dry eye.

Table OS 5: Most Frequent Related AEs (⩾5.0%) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)		
	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety	**Primary Safety Analysis Set**
	All Subjects	**All Subjects**
	(N = 363)	**(N = 108)**
Any treatment-related AE, n (%)	343 (94.5)	**104 (96.3)**
Hyperphosphataemia	224 (61.7)	**80 (74.1)**
Stomatitis	127 (35.0)	**55 (50.9)**
Fatigue	115 (31.7)	**31 (28.7)**
Alopecia	94 (25.9)	**36 (33.3)**
Dry mouth	79 (21.8)	**24 (22.2)**
Dry eye	77 (21.2)	**36 (33.3)**
Dysgeusia	70 (19.3)	**28 (25.9)**
Blood creatinine increased	68 (18.7)	**17 (15.7)**
Decreased appetite	63 (17.4)	**16 (14.8)**
PPES	61 (16.8)	**36 (33.3)**
Diarrhoea	58 (16.0)	**19 (17.6)**
Nausea	57 (15.7)	**11 (10.2)**
Arthralgia	47 (12.9)	**32 (29.6)**
Dry skin	47 (12.9)	**23 (21.3)**
Constipation	46 (12.7)	**11 (10.2)**
Nail disorder	45 (12.4)	**16 (14.8)**
Vomiting	39 (10.7)	**15 (13.9)**
Nail discolouration	36 (9.9)	**20 (18.5)**
Hypercalcaemia	35 (9.6)	**17 (15.7)**
Mucosal inflammation	34 (9.4)	**1 (0.9)**
Blood phosphorus increased	33 (9.1)	**4 (3.7)**
Vision blurred	33 (9.1)	**20 (18.5)**
AST increased	31 (8.5)	**11 (10.2)**
Lipase increased	29 (8.0)	**8 (7.4)**
Onycholysis	29 (8.0)	**14 (13.0)**
Onychomadesis	29 (8.0)	**19 (17.6)**
Pain in extremity	27 (7.4)	**9 (8.3)**
ALT increased	26 (7.2)	**9 (8.3)**
Myalgia	26 (7.2)	**10 (9.3)**
Hypophosphataemia	25 (6.9)	**10 (9.3)**
Dyspepsia	23 (6.3)	**7 (6.5)**
Epistaxis	23 (6.3)	**10 (9.3)**
Abdominal pain	22 (6.1)	**8 (7.4)**
Onychalgia	22 (6.1)	**13 (12.0)**
Anaemia	21 (5.8)	**6 (5.6)**
Weight decreased	21 (5.8)	**6 (5.6)**
Blood ALP increased	20 (5.5)	**5 (4.6)**

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; PPES=palmar-plantar erythrodysaesthesia syndrome. Related AEs reported for ≥5.0% of all subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set are included in this table, sorted in descending order of frequency and then alphabetically for like frequency.

Source: ISS Table 14.3.1.6.6.1; CBGJ398X2204 Primary CSR Table 14.3.1.9.1

Grade 3 or 4 related AEs reported for ≥1.0% of all subjects in descending order of frequency for the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set are provided in Table OS 6. The most common Grade 3 or 4 related AEs (≥5.0%) as assessed by investigators were generally on-target effects of infigratinib and included hyperphosphataemia (7.7%) and stomatitis (5.8%). Grade 4 related AEs reported for ≥2 subjects were increased lipase (3 subjects [0.8%]) and hypophosphataemia (2 subjects [0.6%]).

Table OS-6: Most Frequent Grade 3 or 4 Related AEs (⩾1.0%) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Safety Analysis Set
	All Subjects	All Subjects
	(N = 363)	(N = 108)
Any treatment-related Grade 3	157 (43.3)	54 (50.0)
Hyperphosphataemia	28 (7.7)	12 (11.1)
Stomatitis	21 (5.8)	15 (13.9)
Fatigue	17 (4.7)	4 (3.7)
Hypophosphataemia	15 (4.1)	5 (4.6)
Lipase increased	15 (4.1)	4 (3.7)
PPES	15 (4.1)	7 (6.5)
Hyponatraemia	10 (2.8)	5 (4.6)
ALT increased	8 (2.2)	2 (1.9)
Hypercalcaemia	8 (2.2)	2 (1.9)
AST increased	6 (1.7)	3 (2.8)
Nausea	6 (1.7)	0
Diarrhoea	5 (1.4)	2 (1.9)
Mucosal inflammation	5 (1.4)	1 (0.9)

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; PPES=palmar-plantar erythrodysaesthesia syndrome. Related Grade 3 or 4 AEs reported for ≥1.0% of all subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set are included in this table, sorted in descending order of frequency and then alphabetically for like frequency.

Source: ISS Table 14.3.1.6.9.1; CBGJ398X2204 Primary CSR Table 14.3.1.11.1

Adverse Events of Special Interest (AESI)

Eye disorders (particularly central serous chorioretinopathy/retinal pigment epithelial detachment), disturbance of the Calcium-phosphate homeostasis, tissue calcification and vascular /intravascular mineralisation are important consequences of the mechanism of action of infigratinib. Moreover, since the drug is extensively metabolised potential hepatotoxicity needs to be analysed, which is difficult in a cholangiocarcinoma population applied (please refer to laboratory section).

Eye Disorder and CSR/RPED (central serous chorioretinopathy/retinal pigment epithelial detachment)

Adverse events with respect to eye disorders are of special interest in the target population since they are mostly caused by the on-target toxicity of infigratinib and particularly central serous chorioretinopathy/retinal pigment epithelial detachment (CSR/RPED) may lead to significant impairment

of vision and the consequences may be blinding. Insofar, this adverse event has significant impact on quality of life in the target population. Considering that detection of this complication is not trivial and need special monitoring. 16% of subjects in the primary safety analysis set had an AE of CSR/RPED; median time to onset is assessed between 25 days and 39 days for the primary safety analysis set. CSR/RPED AESIs were often considered related to study drug, which consequently led to dose modifications, treatment with concomitant medications or nondrug therapy, and, in some cases, led to study drug discontinuation. Thus, this issue has an impact on the benefit risk balance.

Calcium-Phosphate Homeostasis

It is acknowledged that hyperphosphataemia is known to be a class effect of FGFR inhibitors, and it may also serve as an actionable on-target indicator to allow monitoring and appropriate dose modifications. Hypophosphataemia, however generally occurred following institution of phosphate binder treatment (ie, was due to unintended overcorrection of hyperphosphataemia); this means it was observed as a secondary adverse events in consequence of the treatment of a infigratinib caused adverse event.

In the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set, 70.8% of subjects had a **hyperphosphataemia AE**. A similar incidence of hyperphosphataemia AEs was reported for the primary safety analysis set (**77.8%).**It should be considered that about the **half of events in the pivotal trial occurring were Grade 3 events** and thereby indicating the trouble caused in the management of the disturbance of Calcium-Phosphate Homeostasis.

Due to the close association to the mode of action of infigratinib, the median time to first onset of hyperphosphataemia (any grade) was short and is reported with 8 days (range: 1 to 78 days); median time to first onset of Grade 3 hyperphosphataemia was 15.0 days (range: 7.0 to 128.0 days); Although no Grade 4 event was reported for hyperphosphataemia, it needs to be considered that hypophosphataemia Grade 3 or 4 when it occurred (8.3% and 1.1%, respectively, in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set), and generally resolved/recovered. No subject discontinued treatment due to hypophosphataemia.).

It needs to be considered that typically, most patients with hyperphosphataemia as well as hypophosphataemia are asymptomatic. Signs and symptoms of acute hyperphosphataemia result from the effects of hypocalcaemia, with patients occasionally reporting symptoms such as muscle cramps, tetany, and perioral numbness or tingling, which are nonspecific and may be mixed up with hyperventilation. In consequence, only blood investigation reveals the dimension of electrolyte disturbance.

Other symptoms include bone and joint pain of even fractures, confusion, pruritus, and rash. More commonly, patients report symptoms also related to the underlying cancer disease as fatigue, shortness of breath, anorexia, nausea, vomiting, and sleep disturbances.

Hypercalcaemia is also a consequence of the hyperphosphataemia induced by infigratinib. The subject incidence of hypercalcaemia in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set (15.4%) was lower than in the subject incidence in the primary safety analysis set (26.9%). Hypercalcaemia had a median time to onset of ≥8 weeks, was generally Grade 1 or 2 in severity, and generally resolved/recovered. Nine subjects had SAEs associated with hypercalcaemia, one of which was also a Grade 4 AE.

Tissue Calcification

Based on the effect of infigratinib on calcium-phosphate homeostasis as well as observations from nonclinical studies, infigratinib has the potential to cause ectopic tissue calcification that could lead to serious complications. It is hypothesised that this toxicity may be mechanistic and specifically related to inhibition of the FGF23/FGFR/Klotho pathway. Programme-wide, 4 subjects were identified with the

search strategy for tissue calcification. These subjects were all from Study CBGJ398X2204. The AEs were calcinosis (2 subjects), calciphylaxis (1 subject), and myocardial calcification (1 subject). These events were deemed related to study drug, led to study drug discontinuation in 2 subjects, were all Grade 1 in severity, generally did not resolve/recover, and had a median time to onset of 165 days (23.6 weeks). However, 1 subject had a clinically significant SAE of calciphylaxis, diagnosed as Peyronie's disease.

Vascular/Intravascular Mineralisation

Localised tissue calcification in blood vessel is leading to occlusive vascular and intravascular mineralisation, similar to tissue calcifications in its mechanistic toxicity, is also a potential on-target effect of infigratinib that could lead to serious complications. Programme-wide, 1 subject was identified with the search strategy for vascular/intravascular mineralisation; however, this complication can only be assessed if symptomatic and it seems that no systematical evaluation regarding this complication was performed. The 1 AE of vascular calcification was Grade 1 and occurred 117 days post-baseline.

Additional adverse events of special interest

Pathological fractures

9 subjects experienced a pathological fracture AESI (5 of them SAE) in the monotherapy safety set. 8 of them had confounding factors that included advanced age, history of previous pathological fractures at sites of bone metastases, osteoporosis, osteopenia, degenerative disc disease, osteoarthritis, and osteomyelitis (note: a subject could have had more than one historical confounder). In addition, 2 of the 9 subjects had traumatic injury as primary cause of the fracture. Given the confounding and contributory factors for these fractures, the investigator considered the 9 cases identified by pathological fracture AESI strategy not related to study drug. Whether the risk of pathological fracture can be assessed as unsupported by the current clinical data needs to be justified more by the applicant in a more detailed argumentation, since this issue may be clearly a consequence of longer dysregulation of the calcium-phosphate homeostasis.

Cardiac toxicity

No off-target effect of infigratinib on QTc prolongation was identified in nonclinical studies. Overall, 4.1% of subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set had an AE from the Torsade de Pointes/QT Prolongation SMQ (broad). The AEs were syncope (2.2%), electrocardiogram QT prolonged (1.4%), electrocardiogram QT interval abnormal (0.3%), and loss of consciousness (0.3%, 1 subject, Grade 4). From the Results of the Exposure (PK)-ECG analysis, infigratinib and its major metabolites, at clinical doses of 125 mg QD 3 weeks on/1 week off, no clinically relevant (ie, >10 ms) effects on the QTcF interval were identified.

Nephrotoxicity

Shift to higher creatinine levels occurred in 30.3% of subjects, but only in few patients (2.5% to Grade 3 or 4). Given the totality of the data, it is acknowledged that it is unlikely that infigratinib contributes to the development of acute kidney injury.

Acute pancreatitis:

Hypercalcaemia may lead to a significant increase of trysin activation and thereby induce pancreatitis. This reasons the special interest regarding this issue in infiratinib's development. Programme-wide 38.1% of subjects had an AE identified by the prespecified search criteria for acute pancreatitis broad SMQ (3.1% had an SAE). In the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set a frequency of 53.7 % and in the primary safety population a higher rate of 58.6 % is reported; mostly Grade 1 or Grade 2 in severity with a median onset time of 15 days, generally recovered/resolved, and were treated with dose modifications/concomitant medications. AEs reported for ≥5% of subjects

included nausea (25.9%), vomiting (21.5%), abdominal pain (15.4%), increased lipase (11.0%), upper abdominal pain (6.6%), and increased amylase (5.8%) The most common Grade 3 events were increased lipase (5.0%), nausea (3.6%), abdominal pain (3.3%), and vomiting (2.8%); the most common Grade 4 event was increased lipase (1.4%); these events of increased lipase were not associated with pancreatitis. However, considering the underlying disease in the target population the events of pancreatitis may be seen as rather not related to infigratinib as assessed by the investigators and mostly due to the progression of underlying malignancy and/or post procedural complications.

3.3.7.3. Serious adverse events, deaths, and other significant events

Serious adverse events

The highest incidences of SAEs were observed in the following SOCs:

- Infections and Infestations (13 subjects [12.0%]),
- Gastrointestinal Disorders (12 subjects [11.1%]),
- General Disorders and Administration Site Conditions (8 subjects [7.4%]), and
- Metabolism and Nutrition Disorders (7 subjects [6.5%]).

The most common SAEs were anaemia (3.7%), hypercalcaemia (3.7%), pyrexia (3.7%), and sepsis (2.8%) (Table OS-7).

Table OS-7: SAEs (⩾1.0%) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy

	125 mg 3 Weeks On/1	Primary
	All Subjects	**All Subjects**
	(N = 363)	**(N = 108)**
Any SAE, n (%)	133 (36.6)	35 (32.4)
Pyrexia	11 (3.0)	4 (3.7)
Sepsis	10 (2.8)	3 (2.8)
Anaemia	9 (2.5)	4 (3.7)
Abdominal pain	8 (2.2)	2 (1.9)
Hypercalcaemia	8 (2.2)	4 (3.7)
Vomiting	8 (2.2)	0
Dyspnoea	7 (1.9)	0
Nausea	7 (1.9)	0
Urinary tract infection	6 (1.7)	1 (0.9)
Acute kidney injury	5 (1.4)	2 (1.9)
Constipation	5 (1.4)	2 (1.9)
Dehydration	5 (1.4)	0
Back pain	4 (1.1)	1 (0.9)
General physical health	4 (1.1)	1 (0.9)
deterioration		
Hyponatraemia	4 (1.1)	1 (0.9)
Pneumonia	4 (1.1)	1 (0.9)

SAE=serious adverse event.
SAEs reported for ⩾1.0% of all subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis
set are included in this table, sorted in descending order of frequency and then alphabetically for like frequency.

Related SAEs reported for ≥2 subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set were abdominal pain, hypercalcaemia, and nausea (3 subjects [0.8%] each) and constipation, hyperphosphataemia, and hypophosphataemia (2 subjects [0.6%] each) (ISS Table 14.3.1.6.8.1).

The 9 subjects who had a treatment-related SAE were two subjects with abdominal pain, and each one subject with hyperphosphataemia, calciphylaxis, hypothyroidism and hypophosphataemia (with hypercalcaemia), constipation, diarrhoea and rash maculo-papular

Deaths

Eighty-nine subjects (89/108; 82.4%) died during the pivotal study CBGJ398X2204: 80 subjects (74.1%) died due to the study indication and 9 subjects (8.3%) died due to other causes.

Of the 89 deaths that occurred during the study, 83 (76.9%) occurred during the post-treatment period, and 6 (5.6%) occurred during the on-treatment period and were described as disease related (cholangiocarcinoma).

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 36 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 and was assessed as not treatment related.

None of the deaths was assessed as drug related by the investigators.

3.3.7.4. Laboratory findings

Clinical Haematology

The AEs reported ≥2.0% subject incidence included anaemia (19.6%), lymphopenia (3.3%), decreased white blood cell count (2.8%), and neutropenia (2.5%) (ISS Table 14.3.1.5.7.1); these events are not unexpected in the oncology population under study. Most hematologic AEs recovered/resolved with either no change to study drug, dose interruption, or dose modification.

Hepatotoxicity

Infigratinib is predominantly metabolised by CYP3A4; as such, its administration may be associated with increases in liver function test parameters. However, in interpreting this data the impact of the underlying cholangiocarcinoma on these parameters has to be taken into account, which makes clear differentiation between drug-related and disease-related effects very difficult. Analyses were performed to evaluate hepatotoxicity (SMQs) and the liver function test parameters AST, ALT, ALP, and bilirubin.

The incidences of AEs for the prespecified minimal critical toxicity of hepatotoxicity are summarised in Table OS-8.

Table OS-8: Summary of AEs for Hepatotoxicity (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

Hepatotoxicity SMQs	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set (N = 363)	Primary Safety Analysis Set (N = 108)
Broad terms, n (%)		
Any AE	100 (27.5)	39 (36.1)
SAE 4	4(1.1)	4 (3.7)
Maximum toxicity		
Grade 1	40 (11.0)	13 (12.0)
Grade 2	28 (7.7)	12 (11.1)
Grade 3	30 (8.3)	12 (11.1)
Grade 4	2 (0.6)	2 (1.9)
Narrow terms, n (%)		
Any AE	82 (22.6)	35 (32.1)
SAE	4 (1.1)	4 (3.7)
Maximum toxicity		
Grade 1	35 (9.6)	15 (13.9)

Table OS-8: Summary of AEs for Hepatotoxicity (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)		
Hepatotoxicity SMQs	**125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set (N = 363)**	**Primary Safety Analysis Set (N = 108)**
Grade 2	21 (5.8)	10 (9.3)
Grade 3	24 (6.6)	8 (7.4)
Grade 4	2 (0.6)	2 (1.9)
AE=adverse event; SAE=serious adverse event; SMQ=Standardised MedDRA Query. SMQ search strategies for minimal critical toxicities are listed in Section 14.1 of the ISS SAP. Source: ISS Tables 14.3.1.5.13.1, 14.3.1.5.14.1, 14.3.1.5.15.1, 14.3.1.5.16.1, 14.3.1.5.17.1, 14.3.1.5.18.1; CBGJ398X2204 Primary CSR Tables 14.3.1.33.13, 14.3.1.33.14		

In the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set, the most common (≥ 5.0% of subjects) AEs in the broad hepatotoxicity SMQ were those related to changes in laboratory values and included increased AST (15.2%), increased ALT (11.3%), increased blood ALP (11.0%), and hypoalbuminaemia (5.2%). Most of the AEs were Grade 1 or Grade 2, some were Grade 3, and very few were Grade 4 (2 subjects; 1 each with hyperbilirubinaemia and increased gamma-glutamyl-transferase).

For the narrow terms search, 4 subjects had SAEs: ascites (2 subjects), hepatic encephalopathy (1 subject), and abnormal hepatic function (1 subject); none were Grade 4 (ISS Table 14.3.1.5.17.1). Hyperlinks to individual Grade 4 AE and SAE subject narratives are provided in Appendix 2.7.4.9.3.

The incidence of high or low laboratory test results for serum chemistry parameters with at least one Grade 3 or 4 result reported is provided in Table OS-9.

Table OS-9: Summary of Liver-Related Serum Chemistry Values Post-baseline (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)		
Category/ Subcategory	**125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set**	**Primary Safety Analysis**
	All Subjects	
	(N = 363)	**(N=108)**
ALP, n (%)		
High (any grade)	286 (78.8)	97 (89.8)
Grade 3	29 (8.0)	10 (9.3)
Grade 4	1 (0.3)	0
ALT, n (%)		
High (any grade)	200 (55.1)	67 (62.0)
Grade 3	19 (5.2)	6 (5.6)
Grade 4	1 (0.3)	1 (0.9)
AST, n (%)		
High (any grade)	257 (70.8)	81 (75.0)
Grade 3	17 (4.7)	4 (3.7)
Grade 4	2 (0.6)	2 (1.9)
Bilirubin, n (%)		
High (any grade)	68 (18.7)	31 (28.7)
Grade 3	15 (4.1)	7 (6.5)
Grade 4	1 (0.3)	1 (0.9)

ALP, ALT, AST, and bilirubin laboratory result shifts of ≥2 grades (worsening) compared with baseline were as follows for the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set:

- Shift to higher ALP levels in 7.4% of subjects (3.9% to Grade 3 or 4)
- Shift to higher ALT levels in 10.7% of subjects (5.5% to Grade 3 or 4).
- Shift to higher AST levels in 7.4% of subjects (4.4% to Grade 3 or 4).
- Shift to higher bilirubin levels in 6.1% of subjects (3.9% to Grade 3 or 4).

Assessment of the Potential for Drug-Induced Liver Injury

In the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set, the incidence of increases in either AST or ALT at >3× ULN and >5× ULN were 21.2% and 7.4%, respectively (Table OS-10). Some subjects had increases in AST or ALT >10× ULN (1.9%), while very few had increases in AST or ALT >20× ULN (0.6%). Total bilirubin was increased ≥2× ULN in 6.1% of subjects.

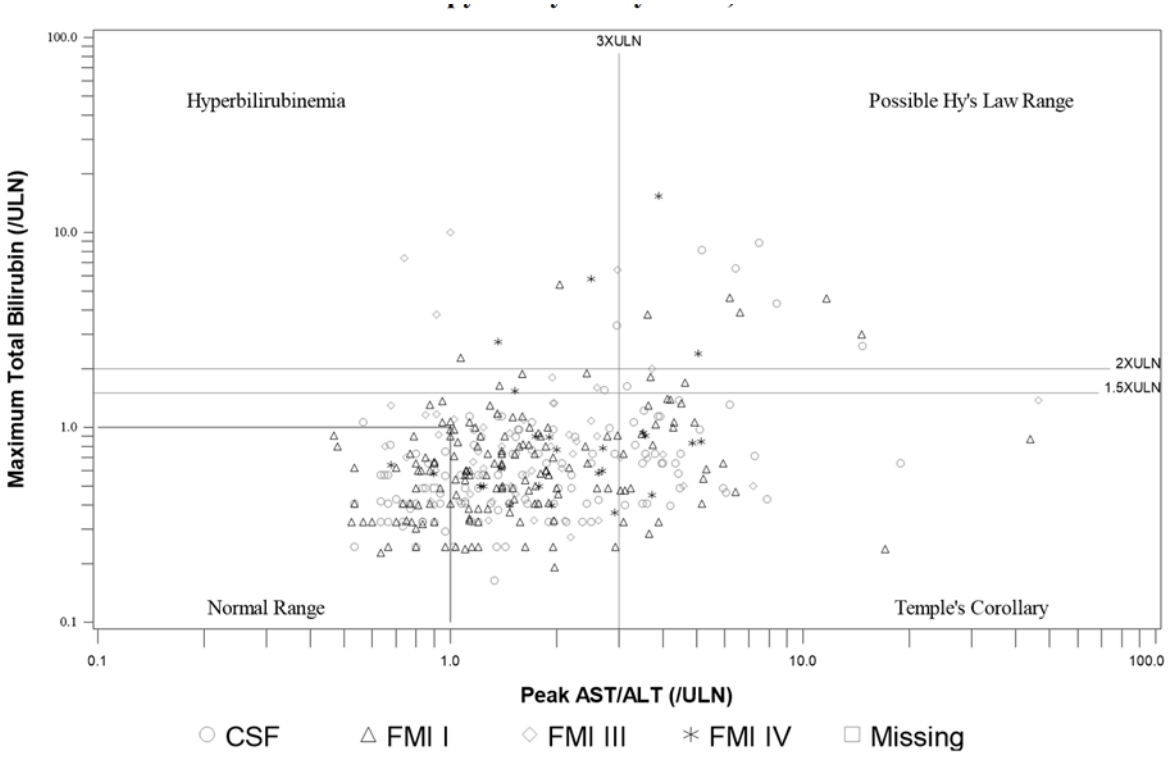
Table OS-10: Summary of Subjects with Increased Liver Parameters According to Worst Value on Treatment (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set	**Primary Safety Analysis**
	(N = 363)	**(N=108)**
AST or ALT		
>3× ULN	77 (21.2)	22 (20.4)
>5× ULN	27 (7.4)	9 (8.3)
>10× ULN	7 (1.9)	3 (2.8)
>20× ULN	2 (0.6)	2 (1.9)
ALT		
>3× ULN	49 (13.5)	17 (15.7)
>5× ULN	20 (5.5)	7 (6.5)
>10× ULN	4 (1.1)	2 (1.9)
>20× ULN	1 (0.3)	1 (0.9)
TBL		
≥2× ULN	22 (6.1)	10 (9.3)
ALP		
>1.5× ULN	197 (54.3)	79 (73.1)
Elevation of AT and TBL		
AT >3× ULN and TBL ≥2× ULN (same day)	10 (2.8)	2 (1.9)
AT >3× ULN and TBL >1.5× ULN (same day)	14 (3.9)	5 (4.6)
AT >3× ULN and TBL ≥2× ULN (on treatment) a	13 (3.6)	4 (3.7)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AT=aminotransferase (ALT and/or AST); TBL=total bilirubin; ULN=upper limit of normal.
a On treatment abnormalities may have occurred on the same day or on different days.
Source: ISS Table 14.3.5.4.1.1; CBGJ398X2204 Primary CSR Table 14.3.5.4.1

Liver laboratory values for the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set are plotted in Figure OS1.

Figure OS-1: Plot of Liver Laboratory Abnormalities (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set)



Source: ISS Figure 14.3.5.5.3.1

Programme-wide, 13 subjects were identified as potential cases of drug-induced liver injury/Hy's Law based on laboratory values of a postbaseline AST/ALT >3× ULN and total bilirubin ≥2.0× ULN identified in samples from the same date. For these patients, baseline conditions, medical history, concomitant medications, hepatic laboratory values, evidence of concurrent cholestasis (ie, ALP <2× ULN), AEs, SAEs, and tumour progression results were reviewed to exclude other reasons for elevations in liver enzymes. Each of these cases were confounded and had alternative etiologies. No drug-induced liver injury/true Hy's Law cases were identified within this analysis. An additional analysis was performed using the criteria of increased AST/ALT >3× ULN and/or total bilirubin ≥2.0× ULN during the on-treatment period (ie, blood samples values were not from the same day). Four additional subjects were identified. Again, each of these cases was confounded and may have had alternative etiologies. Since the provided information is not fully comprehensible, the applicant needs to demonstrate again the details and investigators assessment regarding the patients to be discussed as potential Hy's law cases.

Other Serum Chemistry Analyses

The incidence of high or low laboratory test results for the remaining clinical chemistry parameters that were assessed that had at least one Grade 3 or 4 result reported is provided in Table OS-11:

Table OS-11: Summary of other reported Serum Chemistry Analyses (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)						
Category/ Subcategory	**125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set Formulation**					**Primary Safety Analysis Set**
	CSF	**FMI I**	**FMI III**	**FMI IV**	**All Subjects**	**All Subjects**
	(N = 129)	**(N = 157)**	**(N = 51)**	**(N = 25)**	**(N = 363)**	**(N = 108)**
Albumin						
Low (any grade)	54 (41.9)	60 (38.2)	25 (49.0)	11 (44.0)	150 (41.3)	47 (43.5)
Grade	31 (0.8)	5 (3.2)	1 (2.0)	4 (16.0)	11 (3.0)	5 (4.6)
Potassium						
High (any grade)	22 (17.1)	44 (28.0)	12 (23.5)	4 (16.0)	83 (22.9)	22 (20.4)
Grade 3	0	1 (0.6)	3 (5.9)	0	4 (1.1)	3 (2.8)
Grade 4	1 (0.8)	1 (0.6)	0	0	2 (0.6)	0
Low (any grade)	23 (17.8)	29 (18.5)	19 (37.3)	3 (12.0)	74 (20.4)	30 (27.8)
Grade 3	4 (3.1)	2 (1.3)	1 (2.0)	1 (4.0)	8 (2.2)	3 (2.8)
Grade 4	0	1 (0.6)	0	0	1 (0.3)	0
Magnesium						
High (any grade)	9 (7.0)	19 (12.1)	8 (15.7)	2 (8.0)	38 (10.5)	15 (13.9)
Grade 3	1 (0.8)	4 (2.5)	2 (3.9)	1 (4.0)	8 (2.2)	5 (4.6)
Grade 4	0	0	0	1 (4.0)	1 (0.3)	0
Low (any grade)	32 (24.8)	37 (23.6)	22 (43.1)	10 (40.0)	101 (27.8)	43 (39.8)
Grade 3	0	0	0	1 (4.0)	1 (0.3)	1 (0.9)
Sodium						
High (any grade)	31 (24.0)	29 (18.5)	1 (2.0)	0	62 (17.1)	2 (1.9)
Low (any grade)	83 (64.3)	80 (51.0)	27 (52.9)	11 (44.0)	202 (55.6)	53 (49.1)
Grade 3	24 (18.6)	28 (17.8)	14 (27.5)	3 (12.0)	69 (19.0)	23 (21.3)
Grade 4	0	1 (0.6)	0	0	1 (0.3)	0
Low (any grade)	54 (41.9)	60 (38.2)	25 (49.0)	11 (44.0)	150 (41.3)	47 (43.5)
Grade	31 (0.8)	5 (3.2)	1 (2.0)	4 (16.0)	11 (3.0)	5 (4.6)
Table shows the incidence of high or low laboratory test results for serum chemistry parameters with at least one Grade 3 or 4 result reported. Source: ISS Table 14.3.5.2.1.1; CBGJ398X2204 Primary CSR Table 14.3.5.2.1						

Serum chemistry laboratory result shifts of ≥2 grades (worsening) compared with baseline were as follows for the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set:

- Shift to lower albumin levels in 8.5% of subjects (1.7% to Grade 3 or 4) (ISS Table 14.3.5.6.1.1) (graded results for shifts to higher albumin levels are not available).
- Shift to higher potassium levels in 5.2% of subjects (1.7% to Grade 3 or 4) and shift to lower potassium levels in 17.1% of subjects (2.2% to Grade 3 or 4) (ISS Table 14.3.5.6.9.1).
- Shift to higher magnesium levels in 2.2% of subjects (2.2% to Grade 3 or 4) and shift to lower magnesium levels in 1.4% of subjects (0.3% to Grade 3 or 4) (ISS Table 14.3.5.6.11.1).
- Shift to higher sodium levels in 0.6% of subjects (no Grade 3 or 4) and shift lower sodium levels in 18.2% of subjects (18.2% to Grade 3 or 4) (ISS Table 14.3.5.6.13.1).

Except as described below, overall clinical laboratory evaluations demonstrated no clinically meaningful effect of infigratinib.

3.3.7.5. In vitro biomarker test for patient selection for safety

N/A

3.3.7.6. Safety in special populations

Subgroup analyses were conducted according to race, sex, age, body mass index, region, cancer type, baseline renal function, use of concomitant CYP3A4 inhibitors, use of concomitant CYP3A4 inducers, and AESI-associated medical history. Due to the heterogeneity and the limited size of the available data the reliability of these analyses is challenged. However, at least no unexpected signals indicating a significant need for more clarification were detected from the analyses. As could be expected patients for which a higher exposure or lower tolerability can be presumed (higher age, reduced BMI) a trend for more drug related TEAE seems likely.

Similarly, infigratinib exposure is increased in patients with mild or moderate hepatic impairment as well as in patients with mild (creatinine clearance 60 to 89 mL/min estimated by Cockcroft-Gault) or moderate (creatinine clearance 30 to 59 mL/min) renal impairment compared with healthy subjects and cancer patients with normal hepatic and /or renal function. Thus, recommendation for dose reductions are given in the product information, which may be in principle acceptable considering the available simulations and the absence of further valid contradictory data.

Whether the AE profiles in general were similar between extrinsic factor subgroups according Region, Baseline Renal Function, Use of CYP3A4 Inhibitors or Inducers as described by the applicant is difficult to conclude due to the limited population. However, at least it is acknowledged that no clear trend across categories can be identified and chance findings are also likely to explain some differences observed. Further discussions of this subgroup results are not essential to conclude regarding benefit risk.

3.3.7.7. Immunological events

N/A

3.3.7.8. Safety related to drug-drug interactions and other interactions

Infigratinib is a substrate of CYP3A4 and also a P-gp/BCRP substrate. Strong inhibition of CYP3A4 results in a substantial increase in infigratinib exposure, and moderate CYP3A4 inhibitors may also increase infigratinib exposure. Therefore, co-administration of infigratinib with strong or moderate inhibitors of CYP3A4 is not recommended. Likewise, drugs that are strong inducers of CYP3A4 may result in lower plasma exposures of infigratinib and lead to reduced therapeutic effect; therefore, co-administration with strong or moderate inducers is not recommended. Infigratinib was shown to inhibit CYP3A4 *in vitro*; however, the DDI study with midazolam showed no clinically relevant impact of multiple doses of infigratinib on midazolam PK. Therefore, CYP3A4 substrates may be co-administered with infigratinib.

Infigratinib is also a P-gp and/or BCRP substrate and can be categorised as a low-solubility, moderate to high permeability compound. Consequently, it cannot be excluded that the rate and/or extent of infigratinib absorption is impacted by co-administered inhibitors of P-gp and/or BCRP. However, infigratinib is unlikely to be a substrate of OATP, OAT, or OCT uptake transporters.

Infigratinib has a low potential to inhibit P-gp, BSEP, OCT1, OCT2 and MATE-2K at clinically relevant concentrations and also inhibits BCRP and MATE1 *in vitro*. Clinical interactions with sensitive BCRP and MATE1 substrate thus, cannot be excluded.

Considering the impact and potential need of PPIs in the applied target population, the finding that co-administration of multiple doses of proton pump inhibitor (lansoprazol) decreased infigratinib AUC by 45% and Cmax by 49% and may reduce the efficacy of infigratinib, seems more critical.

A more detailed analysis of the concomitant medications administered during the trial is requested in order to better assess the impact of potentially risky but needed medication in the target population.

Based on findings in an animal study and its mechanism of action, infigratinib can cause foetal harm when administered to a pregnant woman. Women of childbearing potential being treated with infigratinib are advised not to become pregnant and men as well as women must use an effective method of contraception during treatment. With respect to lactation, it is unknown whether infigratinib or its metabolites are excreted in human milk. Insofar, risks to the breastfed child cannot be excluded. Overall, all these issues are sufficiently addressed in the product information.

3.3.7.9. Discontinuation due to adverse events

Adverse Events That Led to Discontinuation of Study Drug

With the applied posology, adverse events that led to discontinuation of study drug were observed in 15.2% of the all monotherapy subjects and slightly higher (19.4) in the primary safety analysis set (Table OS-12).

The most common AEs reported (approximately 1.0% of subjects) included increased blood creatinine, sepsis, fatigue, and increased lipase. Most of them could be attributed to on-target effects of infigratinib (eg, dysgeusia, hypercalcaemia, nail disorder, PPES, subretinal fluid, visual impairment), and probably to a minor degree to the underlying disease (eg, abdominal pain, sepsis).

Table 1. AEs That Led to Discontinuation of Study Drug (⩾2 Subjects) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Analysis Set
	All Subjects	All Subjects
	(N = 363)	(N = 108)
Any AE that led to treatment discontinuation, n (%)	55 (15.2)	21 (19.4)
Blood creatinine increased	*5 (1.4)*	*2 (1.9)*
Sepsis	4 (1.1)	2 (1.9)
Fatigue	3 (0.8)	2 (1.9)
Lipase increased	3 (0.8)	1 (0.9)
Abdominal pain	2 (0.6)	0
AST increased	2 (0.6)	2 (1.9)
Dysgeusia	2 (0.6)	0
Hypercalcaemia	2 (0.6)	0
Nail disorder	2 (0.6)	1 (0.9)
PPES	2 (0.6)	0
Subretinal fluid	2 (0.6)	2 (1.9)
Visual acuity reduced	2 (0.6)	0
Visual impairment	2 (0.6)	0

AE= adverse event; AST=aspartate aminotransferase; PPES=palmar-plantar erythrodysaesthesia syndrome.
AEs that led to discontinuation of study drug reported for ≥2 subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set are included in this table, sorted in descending order of frequency and then alphabetically for like frequency.
Source: ISS Table 14.3.1.6.5.1; CBGJ398X2204 Primary CSR Table 14.3.1.7.1

A remarkable high rate of 71.3% was reported for safety event related dose interruption or dose adjustments in all subjects treated with applied posology.

In the CSR of pivotal trial CBGJ398X2204 it is reported that a similar proportion of 65.7% had an AE that led to a dose interruption and 61.1% had a dose adjustment due to an AE. Moreover, 95.4% of the

subjects in the primary safety analysis set required concomitant medication or non-drug therapy due to an AE.in the target population. From the assessment of the PT it is agreed that the most common AEs that led to dose interruption or dose adjustment (≥5.0% of subjects) included hyperphosphataemia, increased blood creatinine, stomatitis, PPES, fatigue, and increased blood phosphorus. Insofar, the majority of the reported safety events leading to dose interruption and adjustment have to be seen as drug related, since these event can be attributed to on-target effects of infigratinib. Nevertheless, it is also acknowledged that the underlying disease, and/or its consequences may have also at least partially contributed to these events.

Overall, these findings may indicate a low tolerability of the applied posology or the product in general in the applied target population. In addition, it indicates a high need to frequent treatment monitoring in order to avoid harm in the patients in the Rapporteur's view, since the most relevant adverse events caused by electrolyte disorders (hyper/hypophosphataemia, Hypercalcaemia, creatinine increase) are often not related to clear to definitely symptoms. They can only be detected by laboratory assessment. In consequence, damage may have happened before adverse event is diagnosed.

In conclusion treatment with infigratinib resulted in the pivotal SAT in a relative high rate of treatment discontinuation due to adverse events. Whether this is the consequence of an inadequate or intolerable posology needs to be further evaluated.

The applicant is requested to reject the hypothesis that the high rates of treatment discontinuation due to adverse events (19%), AE that led to a dose interruption (65.7%) and dose adjustment due to an AE (61.1%) observed for infigratinib in the SAT CBGJ398X2204, overall indicates an insufficiently justified and hardly tolerable posology.

3.3.7.10. Post marketing experience

The applicant clarified that infigratinib was approved on 28 May 2021 by US FDA (Truseltiq™ capsules, NDA 214622) and on 27 September 2021 in Canada. Whether the product is also already approved in Australia remains unknown, however, submission was made at the time of application in the EU. Therefore, post-marketing data regarding safety should be available and submitted.

3.3.8. Discussion on clinical safety

Safety assessment in this application and the applied indication has to focus on the primary safety data set of 108 subjects with an FGFR2 gene fusion or rearrangement in CBGJ398X2204 Cohort 1, who received at least 1 dose of study drug by the analysis cut-off date of 01 March 2021.

Additional safety analysis is provided from a larger population of 363 subjects who received infigratinib 125 mg QD on a 3 weeks on and 1 week off dosing schedule in trial CBGJ398X2101 (115 subjects with advanced solid malignancies), trial CBGJ398X2201 (26 subjects with glioblastoma), pivotal trial CBGJ398X2204 (All Cohorts 1-3; 108+30), and trial CBGJ398XUS04 (84 subjects with advanced solid or haematological malignancies). However, since exposure in this larger, but very heterogeneous data set was significantly shorter (Median 2.79 months versus 5.59 in the target population), the reliability of this outcome for the applied population seems rather uncertain. Although analysis of differences between both populations is missing, in general outcome is rather similar. This can be expected, since about one third of the included population (n=108/363) reflects the pivotal primary safety population. Moreover, the longer exposure in the 108 patients from the pivotal trial, indicate that exposure in the additional 255 patients must have been very short. Overall, a total of 465 participants have received at least one dose of infigratinib in monotherapy.

In the primary safety analysis set subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS had a median exposure of 5.59 months, and in the 125 mg 3 weeks on/1 week off schedule monotherapy

safety analysis set subjects had a median exposure of only 2.79 months. With respect to the applied indication the relatively short exposure may be explained by a low efficacy in the investigated advance cancer population as well as the need for frequent treatment interruptions due to adverse events a reduced tolerability or inadequate posology. Although it is acknowledged that in the orphan disease population applied the number of treated patients might be sufficient to get a first glance on the safety profile, it needs to be considered that the number of patients being treated for more than 8 months is rather limited (34/108; 31.6%). Thus, long-term toxicity is not evaluable and the follow-up is limited.

In conclusion, it should be considered that the entire safety database is only based on short term exposure from single-arm trials in different target population with a high degree of treatment interruptions and discontinuations. Thus, it remains uncertain, whether the evaluable safety data sufficiently reflect the full safety profile of infigratinib in the claimed indication, even considering the known class-effects of FGFR-2 inhibitors, in the absence of comparative data.

The relative dose intensity is reported with 77.6% (Mean/Median). This may be seen as critical considering that these calculations seems to include the off-treatment period (1week (cycle) of each cycle too and only 27.8% (n=30/108) of the trial population had no dose interruptions. More clarification regarding this issue is requested.

Not surprisingly for an advanced cancer population, almost all patients in study in CBGJ398X2204 Cohort 1 (N=107/108; 99.1%) experienced any adverse events (TEAE). Generally, TEAEs were most frequently reported in the following SOCs; Gastrointestinal Disorders, Metabolism and Nutrition Disorders, General Disorders and Administration Site Conditions, Investigations, and Skin and Subcutaneous Tissue Disorders. Most common TEAEs in patients from the primary safety set (CBGJ398X2204 Cohort 1) were, hyperphosphataemia (76.9), stomatitis (54.6), fatigue (40.7), alopecia (39.8), dry eye (36.1), arthralgia (32.4), dysgeusia (31.5%), constipation (31.5%), dry mouth (25.9%), diarrhoea (25.0%), decreased appetite (24.1%), dry skin (24.1%), hypophosphataemia (23.1%), vomiting (21.3%), nausea (19.4%), abdominal pain (16.7%) pain in extremity (15.7%)and back pain (14.8%). Cholangiocarcinoma itself may cause also gastrointestinal symptoms, which make interpretation of these types of adverse events additionally difficult.

In applied target population the incidence of Grade 3 or 4 AE was 65.7% and of SAEs 32.4%, most frequently reported obviously in the SOCs gastrointestinal disorders and metabolism and nutrition disorders. While most of the AE (96.3%) observed were assessed as possibly treatment-related only 8.3% of the SAEs were defined as treatment-related by the investigators. The most common SAEs in the target population were due to Pyrexia (3.7%), Anaemia (3.7%), Hypercalcaemia (3.7%) and Sepsis (2.8%).

In the overall population, among the 35 participants (32.5%) who had serious TEAEs, the most frequently reported events occurred in the SOCs of gastrointestinal disorders (12.0%) and infections and infestations (11.1%). The most frequently reported serious TEAEs were anaemia, hypercalcaemia and pyrexia (3.7%) and sepsis (2.8%). Serious TEAEs that were considered related to the study drug by the investigator included abdominal pain and due to disturbance of calcium phosphate homeostasis (2.7%) and Rash maculo-papular (0.9%).In addition to the factors already noted, causality assessment for each of these cases was confounded by the general condition of the participant and/or underlying cholangiocarcinoma.

Death occurred in the majority of the patients (82.4%) during the pivotal study CBGJ398X220 until data cut-off, but only 5.6% during the treatment period. None of the deaths was assessed as drug related by the investigators.

A remarkable high rate of 71.3% was reported for safety event related dose interruption or dose adjustments in all subjects treated with applied posology. In the CSR of pivotal trial CBGJ398X2204 it is

reported that a similar proportion of 65.7% had an AE that led to a dose interruption and 61.1% had a dose adjustment due to an AE. Moreover, 95.4% of the subjects in the primary safety analysis set required concomitant medication or non-drug therapy due to an AE.in the target population. Again hyperphosphataemia, increased blood creatinine, stomatitis, PPES, fatigue, and increased blood phosphorus were the main causes for treatment interruption. Insofar, the majority of the reported safety events leading to dose interruption and adjustment have to be seen as drug related, since these event can be attributed to on-target effects of infigratinib.

The high rates of treatment discontinuation due to adverse events (19%), AE that led to a dose interruption (65.7%) and dose adjustment due to an AE (61.1%) observed for infigratinib in the SAT CBGJ398X2204, may indicate an insufficiently justified and hardly tolerable posology, which needs further clarification.

Similar outcome was observed in the larger supportive population of the "125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set".

Incidences of the most common AEs according SOCs are: Gastrointestinal Disorders (84.0%), Metabolism and Nutrition Disorders (82.4%), General Disorders and Administration Site Conditions (68.6%), Investigations (58.4%), and Skin and Subcutaneous Tissue Disorders (57.6%).

Grade 4 AEs reported for ≥2 subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set were sepsis (8 subjects [2.2%]), increased lipase (5 subjects [1.4%]), hypophosphataemia (4 subjects [1.1%]), septic shock (2 subjects [0.6%]), respiratory failure (2 subjects [0.6%]), and cataract (2 subjects [0.6%]).

The most common related AEs (≥20.0%) as assessed by investigators in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set were generally on-target effects of infigratinib and included hyperphosphataemia, stomatitis, fatigue, alopecia, dry mouth, and dry eye.

The most common Grade 3 or 4 related AEs (≥5.0%) as assessed by investigators were generally on-target effects of infigratinib and included hyperphosphataemia (7.7%) and stomatitis (5.8%). Grade 4 related AEs reported for ≥2 subjects were increased lipase (3 subjects [0.8%]) and hypophosphataemia (2 subjects [0.6%]).

Notable differences between the CSF, FMI I, and FMI III formulations (defined as AEs that had at least a 10.0% incidence for each formulation and showed a ≥2-fold difference in incidence between formulations) were stomatitis, dry eye, and pain in extremity, all of which occurred more frequently with the FMI III formulation. However, differences may, in part, be based on the longer duration of exposure for subjects who took the FMI III formulation (median, 6.3 months) versus the CSF and FMI I formulations (median, 1.6 and 3.5 months, respectively) and inclusion of other cancer populations. In general, no notable effect on the overall AE profile can be derived from the extensively reported safety details according to formulations administered and interpretation of reported differences is not meaningful in the Rapporteur's view.

TEAEs leading to fatal outcome were reported in 6/383 patients in the "125 3weeks on/1 week off schedule monotherapy analysis set, these deaths during the treatment period were described as not attributed to the study indication due to intestinal ischemia, coma, and respiratory failure (1 subject each), while in the three others no details were provided.

No clinically meaningful difference was observed in the incidence of AEs that led to discontinuation of study drug in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set (15.2%) and the primary safety analysis set (19.4%); the most common AEs reported (approximately 1.0% of subjects) included increased blood creatinine, sepsis, fatigue, and increased lipase. Generally, AEs that led to discontinuation of study drug could be attributed to on-target effects of infigratinib (eg, dysgeusia,

hypercalcaemia, nail disorder, PPES, subretinal fluid, visual impairment), underlying disease (e.g., abdominal pain), and/or its consequences (e.g., sepsis).

AESIs

Eye disorders (particularly central serous chorioretinopathy/retinal pigment epithelial detachment), disturbance of the Calcium-phosphate homeostasis, tissue calcification and vascular /intravascular mineralisation are important consequences of the mechanism of action of infigratinib. Moreover, since the drug is extensively metabolised potential hepatotoxicity needs to be analysed, which is difficult in a cholangiocarcinoma population applied.

Adverse events with respect to eye disorders are of special interest in the target population since they are mostly caused by the on-target toxicity of infigratinib and particularly central serous chorioretinopathy/retinal pigment epithelial detachment (CSR/RPED) may lead to significant impairment of vision and the consequences may be blinding. Insofar, this adverse event has significant impact on quality of life in the target population. Considering that detection of this complication is not trivial and need special monitoring. 16% of subjects in the primary safety analysis set had an AE of CSR/RPED; median time to onset is assessed between 25 days and 39 days for the primary safety analysis set. CSR/RPED AESIs were often considered related to study drug, which consequently led to dose modifications, treatment with concomitant medications or nondrug therapy, and, in some cases, led to study drug discontinuation. Thus, this issue has an impact on the benefit risk balance.

Another important class-effect toxicity of FGFR inhibitors concerns induction of disturbance in the Calcium-Phosphate Homeostasis. 77.8% of the pivotal target population had hyperphosphataemia adverse events; half of events observed in the pivotal trial occurring were > Grade 3 events and had an onset during the first weeks of therapy. Although no Grade 4 event was reported for hyperphosphataemia, Grade 3 or 4 adverse events were reported for hypophosphataemia in 12.0% and 0.9% of the primary safety population. It needs to be considered that these adverse events are the consequence of the treatment of the infigratinib induced hyperphosphataemia. Moreover, since all patients at the end discontinued the infigratinib therapy it is not reassuring that all events are reported as resolved/recovered. Moreover, 26.9% of the patients in the target population developed hypercalcaemia owing to hyperphosphataemia; 9 subjects had SAEs due to hypercalcaemia. This clarifies that infigratinib has the potential to cause ectopic tissue calcification that could lead to serious complications. Whether it is reassuring that only 4 subjects with tissue calcification were identified (all from Study CBGJ398X2204) may be challenged, since the applicant's strategy to evaluate this issue remains unknown at present and needs further discussion. The AEs were calcinosis (2 subjects), calciphylaxis (1 subject), and myocardial calcification (1 subject) and led to study drug discontinuation in 2 subjects. Insofar, the risk from infigratinib-induced disturbance in calcium-phosphate homeostasis may be easily underestimated; in particular, since symptoms are often unspecific and only detected by regular laboratory monitoring; however, even laboratory monitoring under trial conditions was not sufficient to avoid serious complications of the phosphate lowering agents needed to control the drug-related hyperphosphataemia. Insofar, this toxicity clearly is clinically relevant risk that needs to be balanced. Whether the risk of pathological fracture as observed in 9 subjects can be assessed as unsupported by the current clinical data needs to be justified more by the applicant in a more detailed argumentation, since this issue may be another consequence of longer dysregulation of the calcium-phosphate homeostasis. Similarly, the applicant should clarify whether data on infiratinib's impact on Vitamin D and parathyroid hormone are available.

Hypercalcaemia may also lead to a significant increase of trysin activation and thereby induce acute pancreatitis. However, considering the underlying disease in the target population, it seems difficult to further evaluate the high event rate of 58.6% and the 1.4 % of Grade 4 events with increase lipase reported. According to the investigator's assessment, events of pancreatitis may be seen as rather not

related to infigratinib and mostly due to the progression of underlying malignancy and/or post procedural complications. Whether this is reliable remains unknown at the end.

No clear signal for an increased cardiac and renal toxicity can be derived from the data at present. Interestingly, the occurrence of nail toxicity is currently not addressed in the submitted documents, but further analysis of the clinically relevant FGFR inhibitor associated class effect toxicity should be provided.

With respect to the laboratory findings provided, the question whether infigratinib has an intrinsic hepatotoxicity needs further attendance. Infigratinib is predominantly metabolised by CYP3A4; as such, its administration may be associated with increases in liver function test parameters and also with potential drug-induced liver injury. However, in interpreting the data available in the target population the impact of the underlying cholangiocarcinoma on the relevant liver parameter hampered any clear differentiation between drug-related and disease-related effects very difficult. In total, 13 subjects were identified during clinical development as potential cases of drug-induced liver injury according Hy's Law. However, each of these cases is reported to be confounded and may have had alternative aetiologies. Since the provided information is not fully comprehensible, the applicant needs to provide and discuss the relevant details and to justify the conclusion. No other result regarding the laboratory monitoring needs to be discussed.

DDI: Infigratinib is a substrate of CYP3A4 and also a P-gp/BCRP substrate. Strong inhibition of CYP3A4 results in a substantial increase in infigratinib exposure, and moderate CYP3A4 inhibitors may also increase infigratinib exposure. Therefore, co-administration of infigratinib with strong or moderate inhibitors of CYP3A4 is not recommended. Similarly, strong inducers of CYP3A4 may result in lower plasma exposures of infigratinib thereby leading probably to reduced therapeutic effect and need to be avoided. Moreover, infigratinib has a low potential to inhibit P-gp, BSEP, OCT1, OCT2 and MATE-2K at clinically relevant concentrations and also inhibits BCRP and MATE1 *in vitro*. Clinical interactions with sensitive BCRP and MATE1 substrate thus, cannot be excluded. More relevant may be the finding that co-administration of multiple doses of proton pump inhibitor (lansoprazol) decreased infigratinib AUC by 45% and Cmax by 49% and probably reduce the efficacy of infigratinib. Taken into account the frequent need for PPIs in the cholangiocarcinoma population, this seems more critical. Considering that the severely ill cancer population is in need for potentially drug-interacting products, an analysis of the impact of the different DDI on needed concomitant medication was not fully evaluable; this information is requested in order to identify potentially needed conflicting concomitant medications.

Based on findings in an animal study and its mechanism of action, infigratinib can cause foetal harm when administered to a pregnant woman. Women of childbearing potential being treated with infigratinib are advised not to become pregnant and men as well as women must use an effective method of contraception during treatment. With respect to lactation, it is unknown whether infigratinib or its metabolites are excreted in human milk. Insofar, risks to the breastfed child cannot be excluded. Overall, all these issues are sufficiently addressed in the product information.

Since the product is approved at least in the US, Canada and potentially also in Australia, the applicant is requested to summarise the post-marketing experience available regarding safety.

Additional expert consultation

Not at present.

Assessment of paediatric data on clinical safety

N/A

Additional safety data needed in the context of a conditional MA

Not to discuss at this stage of assessment.

3.3.9. Conclusions on clinical safety

Entire safety database is based on limited, non-comparative data from single-arm trials in different diseases with limited follow-up period. The total safety database for the applied 125 mg 3 weeks on/ 1 week off monotherapy treatment consists of 363 patients; from them only 108 represent the applied cholangiocarcinoma target population with FGFR2 rearrangement or fusion. Exposure was rather short (Median5.59 in the target population/ Median 2.79 months in the larger population) and treatment needs to frequently interrupted and dose was reduced in more than two third of the trial population.

These findings may allow a first glance on the limitations and uncertainties of risk assessment at present.

Moreover, clinical experience with other FGFR2 inhibitors is also very limited, which indicate difficulties in the identification of additional human class-effect risks. Similarly, assessment of causality regarding the adverse events beside the non-clinical signals and the known class effects for FGFR2 inhibitors is difficult to confirm, as they can be due to the drug effect, disease, aging or other factors.

The limited safety data available indicate safety non-negligible profile for infigratinib, as characterised by a high incidence and grading of the events reported, mainly related to metabolic disorders, gastrointestinal disorders and skin and subcutaneous tissue disorders. In particular, the potential risk for vision and blinding as a consequence and complications of disturbance of Calcium-Phosphate Homeostasis, need to be balanced, while the risk for drug-induced liver injury remains not evaluable at present. Clinical consequences at short and long-tem, management strategies and preventability measures are needed to be discussed.

In addition, the characterisation of the safety profile in the applied posology is hampered due to the fact that in the pivotal study X2204 most CCA patients need toxicity-driven sustainable dose reductions shortly after start of treatment and were not able to return to the 125 mg dose (mean relative dose intensity was ~78%).

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	**Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED)** **Imbalance of calcium/phosphorus homeostasis**
Important potential risks	**Embryo-foetal toxicity**
Missing information	**Use in patients with severe hepatic impairment** **Use in patients with severe renal impairment**

3.4.1.1. Discussion on safety specification

The summary of the safety concerns are largely acceptable, however some questions remain to be answered by the MAH. Furthermore, some modifications of the list of safety concerns are required.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification,

The CHMP considers that the following issues should be addressed:

- In Part II Module SI of the RMP the applicant constitutes that: "Globally, the average age at diagnosis of metastatic cholangiocarcinoma is >50 years (Blechacz 2017)[1]. In Western industrialised nations, the median age at presentation is 65 years." Furthermore, in the EU-SmPC section 4.6 the contraception for men and women of childbearing potential is strongly recommended. Thus, the applicant is requested to critically discuss if "Embryo-foetal toxicity" should be classified as important potential risk or can be removed from the list of safety concerns.
- The helpful comment from MS is acknowledged. We have modified the OC concerning the important potential risk "Embryo-foetal toxicity" accordingly:
  The applicant is requested to explain the plan for a future evaluation of the important potential risk "Embryo-foetal toxicity". More precisely, the applicant is asked to provide detailed information on the studies in which this risk is further characterised.
- Which advice would the applicant give to HCPs intending to treat patients with severe renal impairment and which measure does the applicant propose to gather relevant information to explore the impact of infigratinib in patients with severe renal impairment?
- Concerning the missing information "Use in patients with severe hepatic impairment", routine pharmacovigilance is proposed for monitoring this missing information and the EU-SmPC proposes a dose reduction for subjects with mildly or moderately reduced liver function. Which dose does the applicant propose for patients with severe hepatic impairment?
- For pemigatinib, "acute kidney injury" is listed as important potential risk. Thus, the applicant is requested to discuss, if a class effect is applicable and e.g. kidney injury can be classified as relevant important potential risk for infigratinib, although clinical data do not suggest this currently.

The CHMP considers that "Pathologic fractures" should also be a safety concern:

- Based on the pharmacological mechanism of infigratinib (inhibition of FGFR1, FGFR2, and FGFR3) and the detection of an impact on bone density and strength in animal models, it is conceivable that those effects will also occur in patients treated for a longer period with infigratinib. Although a remission of bone effects was reported in animals, it is likely that remission in elderly and heavily pre-treated patients will not or just partially appear. It is acknowledged that none of the fracture-related AEs in clinical trials was related to treatment with infigratinib. Nevertheless, "pathologic fractures" should be regarded as important potential risk and included in the list of safety concerns.

3.4.2. Pharmacovigilance plan

The applicant proposed no additional routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

[1] Blechacz B. Cholangiocarcinoma: current knowledge and new developments. Gut Liver. 2017;11(1):13-26.

Specific adverse reaction follow-up questionnaires regarding the safety concern embryo-foetal toxicity are proposed:

- A pregnancy follow-up questionnaire to collect and evaluate specific data related to embryo-foetal toxicity in the post-marketing period.

Summary of planned additional PhV activities from RMP

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PRAC Rapporteur assessment comment:

Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) and Imbalance of calcium/phosphorus homeostasis

For the two important identified risks: 'Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED)' and 'Imbalance of calcium/phosphorus homeostasis,' both are known class effects of FGFR inhibition and both risks have also been confirmed in nonclinical and clinical studies of infigratinib. In clinical trials CSR/RPED was observed in 11% of 363 patients, hyperphosphataemia was reported as an adverse event in 71% of 363 patients and hypercalcaemia was reported in 15% of 363 patients treated with infigratinib. Overall, the risks appear sufficiently characterised, and thus it is agreed that routine pharmacovigilance activities remain sufficient for further characterisation of these two safety concerns.

Embryo-foetal toxicity

Due to findings from an animal study showing foetal harm, women of childbearing potential and men with women partners of childbearing potential should avoid pregnancy and use effective contraception during treatment with infigratinib and for 1 month following completion of therapy. Therefore, the risk of exposure during pregnancy is expected to be very limited. Provided applicant's satisfactory response to the CHMP rapporteur's OC regarding the follow-up of this risk, it could be agreed that routine pharmacovigilance activities including a pregnancy follow-up questionnaire would be considered sufficient for the potential identified risk Embryo-foetal toxicity.

Use in patients with severe renal and hepatic impairment

According to the RMP, based on the available PK data from Study QBGJ398-107 and the population PK model for subjects with mild hepatic impairment (Child-Pugh A) and moderate hepatic impairment (Child-Pugh B), it is expected that infigratinib exposure would be increased in patients with severe hepatic impairment leading to an increased risk of adverse reactions. Likewise, based on the available PK data

from Study QBGJ398-110 and the population PK modelling and simulation for subjects with mild and moderate renal impairment, it is expected that infigratinib exposure would be increased in patients with severe renal impairment leading to an increased risk of adverse reactions.

In light of the above, the applicant is requested to discuss why routine pharmacovigilance activities are considered sufficient to explore the impact of infigratinib in patients with severe renal impairment and in patient with severe hepatic impairment.

Additional safety concerns proposed by the CHMP rapporteur

For the safety concerns proposed by the CHMP rapporteur Acute Kidney Injury and Pathological Fractures, the applicant should consider both routine and additional pharmacovigilance activities and risk minimisation measures.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan could be acceptable to identify and characterise the risks of the product provided that the requests for supplementary information in section 9 are satisfactorily addressed.

The PRAC Rapporteur also considered that routine PhV could be sufficient to monitor the effectiveness of the risk minimisation measures provided that the requests for supplementary information in section 9 are satisfactorily addressed.

3.4.3. Risk minimisation measures

Please refer to the updated PRAC Rapp RMP AR.

Summary of risk minimisation measures of the RMP are summarised in below table.

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Central serous retinopathy/ retinal pigment epithelial detachment (CSR/RPED) (Important identified risk)	Routine risk communication: - *Adverse reaction in section 4.8 of SmPC* - *Side effect in section 4 of PL* Routine risk minimisation activities recommending specific clinical measures to address the risk: - *Guidance for dose modifications for RPED based on severity including continuing infigratinib at the current dose if RPED resolves within 14 days, temporarily withholding infigratinib if RPED does not resolve within 14 days and then resuming at previous or a lower dose, and permanently discontinuing infigratinib if RPED with significant vision loss occurs at lowest dose (50 mg) in section 4.2 of SmPC* - *Warning that infigratinib can cause RPED with descriptions of the symptoms and the cases of RPED observed in the clinical study in section 4.4 of SmPC*

	- *Recommendation to perform an ophthalmic examination including optical coherence tomography prior to initiation of therapy, at 1 month, at 3 months, and then every 3 months thereafter during treatment and urgently at any time for visual symptoms in section 4.4 of SmPC* - *Warning to carefully consider use of infigratinib in patients with clinically significant medical eye disorders, such as retinal disorders, including but not limited to, central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment in section 4.4 of SmPC* - *Guidance to recommend caution when driving or operating machines as fatigue and visual disturbances have been associated with infigratinib in section 4.7 of SmPC* - *Guidance for the patient to talk to their doctor or pharmacist before taking infigratinib if they have vision or eye problems in section 2 of PL* - *Guidance that eye examinations are recommended before starting infigratinib treatment, after 1 month and 3 months of treatment, and every 3 months thereafter or immediately if any visual symptoms occur, including flashes of light, visual disturbances or dark spots in section 2 of PL* - *Guidance for patients to tell their doctor straight away if they experience any symptoms with their vision in section 2 of PL* - *Guidance that infigratinib can cause side effects such as fatigue or visual disturbances and not to drive or operate machinery if this happens in section 2 of PL* Other routine risk minimisation measures beyond the Product Information: - *Legal status: restricted medical prescription*
Imbalance of calcium/phosphorus homeostasis (Important identified risk)	Routine risk communication: - *Guidance that phosphate-lowering therapy was used by 80.6% of patients during treatment with infigratinib in sections 4.4 and 4.8 of SmPC* - *Adverse reactions in section 4.8 of SmPC* - *Guidance that infigratinib increased serum phosphate levels as a consequence of FGFR inhibition and that phosphate-lowering therapy and dose modifications were permitted to manage hyperphosphataemia in the clinical studies in section 5.1 of SmPC* - *Guidance that changes in calcium/phosphorus homeostasis and ectopic tissue mineralisation were observed in nonclinical studies in section 5.3 of SmPC*

	- *Side effects in section 4 of PL* Routine risk minimisation activities recommending specific clinical measures to address the risk: - *Guidance that a low-phosphate diet should be initiated and to consider adding phosphate-lowering therapy in all patients when serum phosphate level is >5.5 mg/dL, and to adjust the dose of phosphate-lowering therapy until serum phosphate level returns to <5.5 mg/dL in section 4.2 of SmPC* - *Guidance to hold the phosphate-lowering therapy during the week off within each infigratinib treatment cycle or if serum phosphate level falls below normal range in section 4.2 of SmPC* - *Guidance for infigratinib dose modifications and management depending on severity including monitoring serum phosphate, initiating phosphate-lowering therapy or adjusting the dose as needed, withholding infigratinib until level returns to ≤5.5 mg/dL, and permanently discontinuing infigratinib if serum phosphate levels have life threatening consequences or urgent intervention indicated eg, dialysis in section 4.2 of SmPC* - *Warning that hyperphosphataemia is a pharmacodynamic effect expected with infigratinib and that prolonged hyperphosphataemia can cause precipitation of calcium-phosphate crystals that can lead to soft tissue mineralisation, cutaneous calcinosis, nonuremic calciphylaxis, vascular calcification, and myocardial calcification in section 4.4 of SmPC* - *Recommendation for management of hyperphosphataemia including dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required in section 4.4 of SmPC* - *Guidance for the patient to talk to their doctor or pharmacist before taking infigratinib if they have been told they have an increase or decrease of a mineral in their blood called phosphorus in section 2 of PL* Other routine risk minimisation measures beyond the Product Information: - *Legal status: restricted medical prescription*
Embryo-foetal toxicity (Important potential risk)	Routine risk communication: - *Guidance that there are no available data from the use of infigratinib in pregnant women in section 4.6 of SmPC* - *Guidance that a study in animals has shown reproductive toxicity in sections 4.6 and 5.3 of SmPC* Routine risk minimisation activities recommending specific clinical measures to address the risk:

	- *Warning that infigratinib can cause foetal harm and that women of childbearing potential treated with infigratinib should be advised not to become pregnant and men treated with infigratinib should be advised not to father a child during treatment in sections 4.4 and 4.6 of SmPC* - *Guidance for women of childbearing potential and male patients with female partners of childbearing potential to use effective contraception during infigratinib treatment and for 1 month following completion of therapy in sections 4.4 and 4.6 of SmPC* - *Guidance that a pregnancy test should be performed before treatment initiation to exclude pregnancy in sections 4.4 and 4.6 of SmPC* - *Guidance that based on animal data and the pharmacology of infigratinib, infigratinib should not be used during pregnancy unless the clinical condition of the women requires treatment with infigratinib in section 4.6 of SmPC* - *Guidance for the patient to ask their doctor or pharmacist for advice before taking this medicine if they are pregnant, think they may be pregnant or are planning to have a baby in section 2 of PL* - *Warning that infigratinib may harm the unborn baby and should not be used during pregnancy unless the patient is told otherwise by their doctor in section 2 of PL* - *Guidance that a pregnancy test should be performed before initiating treatment in section 2 of PL* - *Guidance that women being treated with infigratinib should not become pregnant and therefore women who could become pregnant must use effective contraception during treatment and for at least 1 month after the last dose of infigratinib and to talk to their doctor about the most suitable contraception in section 2 of PL* - *Guidance that men should avoid fathering a child and that they must use effective contraception during treatment and for at least 1 month after the last dose of infigratinib in section 2 of PL* Other routine risk minimisation measures beyond the Product Information: - *Legal status: restricted medical prescription*
Use in patients with severe hepatic impairment (Missing information)	Routine risk communication: - *Guidance that the effect of severe hepatic impairment on infigratinib exposure is unknown in section 5.2 of SmPC* Routine risk minimisation activities recommending specific clinical measures to address the risk: - *None* Other routine risk minimisation measures beyond the Product Information:

	- *Legal status: restricted medical prescription*
Use in patients with severe renal impairment (Missing information)	Routine risk communication: - *Guidance that the effect of severe renal impairment or renal dialysis in endstage renal disease on infigratinib exposure is unknown in section 5.2 of SmPC* Routine risk minimisation activities recommending specific clinical measures to address the risk: - *None* Other routine risk minimisation measures beyond the Product Information: - *Legal status: restricted medical prescription*

PRAC Rapporteur assessment comment:

Central serous retinopathy/ retinal pigment epithelial detachment (CSR/RPED)

According to RMP section SVII.1.2, CSR/RPED is a serious condition that if not promptly treated may cause persistent or recurrent serous macular detachment, with subsequent progressive visual loss. In clinical trials CSR/RPED was observed in 11% of 363 patients treated with infigratinib and CSR/RPED was severe in 0.8% of patients.

According to RMP section SVII.3.1, CSR/RPED cannot be prevented but it can be minimised through increased healthcare professional awareness, patient monitoring (regular optical coherence tomography (OCT)) and risk management in clinical practice. Dose reduction, as outlined in SmPC section 4.2, is part of the management.

HCP and patient awareness as well as patient monitoring are thus essential to minimise this serious risk.

In this regard, the applicant is asked to further justify the scientific grounds for the statement that routine risk minimisation activities are considered sufficient to manage the safety concern CSR/RPED. Among the observed CSR/RPED cases in the clinical trials, how many were initially identified via regular monitoring procedures and how many of the cases were initially identified based on patients' own awareness? What will be the expected level of risk reduction with the monitoring schedule currently outlined in the SmPC?

Imbalance of calcium/phosphorus homeostasis

Minimising overcorrection of hyperphosphataemia

In clinical trials hyperphosphataemia was reported as an AE in 71% of 363 patients treated with infigratinib of which some additionally experienced hypophosphataemia due to unintended overcorrection of hyperphosphataemia.

The risk of unintended overcorrection of hyperphosphataemia that results in hypophosphataemia seems significant based on the clinical trial data, but there is currently no direct specific clinical measure in place to address this risk and it is not at present clear from SmPC section 4.8 that the ADR hypophosphataemia seems to occur secondary to the overcorrection of hyperphosphataemia. The applicant is asked to propose strengthened routine risk minimisation measures for the risk of hypophosphataemia caused by unintended overcorrection of hyperphosphataemia.

Evidence on diet for minimising imbalances of calcium/phosphorus homeostasis

Imbalances of calcium/phosphorus homeostasis can be life-threatening if left untreated. According to RMP SVII.3, they can be managed in clinical practice through increased awareness, patient monitoring and adhering to the infigratinib product information.

Similarly, as for the CSR/RPED risk, the risk management of these phosphorus/calcium imbalances is therefore essential.

It is noticed that in section 4.2 of the infigratinib SmPC, it is recommended to initiate a low-phosphate diet in all patients, yet this recommendation is not reflected in the PL. It is therefore unclear how a patient should accommodate with this recommendation.

Moreover, according to a Cochrane review on the subject, it seems like there exists only limited low quality evidence available for the effect of low-phosphate diet *(Liu Z, Su G, Guo X, Wu Y, Liu X, Zou C, Zhang L, Yang Q, Xu Y, Ma W. Dietary interventions for mineral and bone disorder in people with chronic kidney disease. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD010350. DOI: 10.1002/14651858.CD010350.pub2).*

The applicant is asked to discuss the scientific grounds for recommending a low-phosphate diet to all patients including the literature supporting low-phosphate diet as a feasible risk management strategy. Depending on the outcome of this discussion, the applicant should propose improved patient information either by PL text or by means of patient-oriented educational material about low-phosphor diet.

Embryo-foetal toxicity

Considering that exposure in pregnancy is low as the median age at presentation with metastatic cholangiocarcinoma is 65 years in Western industrialised nations and the warning against use during pregnancy as well as use of contraceptives during treatment, the risk minimisation measures proposed are considered sufficient.

Use in patients with severe hepatic and renal impairment

No risk minimisation measures for use in patients with severe and renal impairment are suggested by the applicant. However, the applicant should consider if it is feasible to include a precautionary advice against use, extrapolated from the observations on patients with moderate renal and hepatic impairment in which dose reductions are required. As suggested by the CHMP rapporteur, risk minimisation measures on dose reductions for use in patients with severe hepatic and renal impairment should be considered.

Additional risk minimisation measures

The applicant considered that routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product and proposed no additional risk minimisation measures.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

the proposed risk minimisation measures are not sufficient to minimise the risks of the product and supplementary risk minimisation measures could be required relating to:

- Central serous retinopathy/ retinal pigment epithelial detachment (CSR/RPED)
- Imbalance of calcium/phosphorus homeostasis
- Use in patients with severe hepatic and renal impairment

3.4.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.1 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

The applicant/Proposed Future MAH has submitted a signed Summary of the applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS/Rapporteur considers the Summary acceptable.

3.5.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. <The applicant did <not> request an alignment of the PSUR cycle with the international birth date (IBD)>. <The IBD is {DD.MM.YYYY.}>.

The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

4. Non-Conformity with agreed Paediatric Investigation Plan

N/A

5. Benefit risk assessment

5.1. Therapeutic Context

The purpose of the current submission is to seek conditional marketing authorisation (CMA) for Febseltiq (infigratinib) in the following indication applied:

Febseltiq monotherapy is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

5.1.1. Disease or condition

Biliary tract cancers, including intrahepatic and extrahepatic cholangiocarcinoma (CCA) and gallbladder cancers, are tumours characterised by an aggressive disease course and poor clinical outcome. CCA is quite rare, with 1 to 2 patients per 100,000 in the EU and the US and commonly present at an advanced disease stage with a 5-year survival rate reported to be low and that varies by stage: 50% for stage I, 30% for stage II, 10% for stage III, and 0% for stage IV (Valle et al 2017).

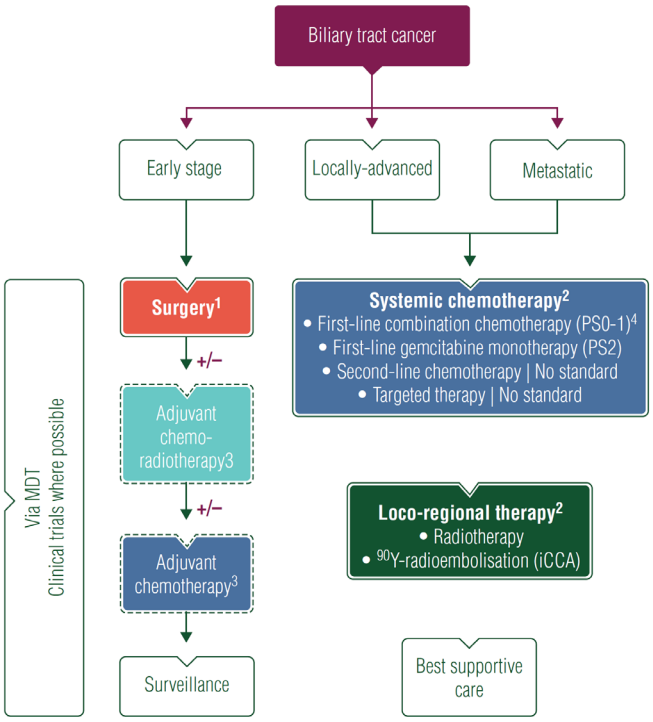
However, CCA is a very heterogeneous population and patients with FGFR2 rearrangement or fusion may have a better prognosis that patients without FGFR genetic aberration (Churi et al, 2014; Jain et al, 2018). In the largest published retrospective analysis of 377 cholangiocarcinoma patients treated across four major academic cancer centres (95 with FGFR genetic alterations, of which 63 had FGFR2 fusions),

overall survival (OS) was prolonged for patients with FGFR genetically altered cholangiocarcinoma versus WT, when not accounting for use of FGFR inhibitor therapy (median OS of 37 months vs 20 months, P<.001; Jain 2018). However, it is full acknowledged that this analysis may also have hidden sources. Nevertheless, it is agreed with the authors that FGFR GAs in general may be associated with a relatively indolent disease course and survival benefit from FGFR inhibitors in the FGFR 2 subpopulation may only be reliably assessed from a prospective, randomised controlled trial; SAT data may be only sufficiently informative, if results are outstanding.

Moreover, it is considered that although FGFR2 GA has been used as a predictive biomarker in these trials, it is clear that not all FGFR fusion CCAs respond to FGFR inhibitors, and additional predictive biomarkers may be needed to better understand treatment responses. Furthermore, the relationship between FGFR GAs with tumour location (primary tumour v metastases) and uncommon histologies such as undifferentiated cancers and hepatocholangiocarcinoma deserves further study (Jain et al, 2018).

5.1.2. Available therapies and unmet medical need

The following algorithm illustrates the management of patients with biliary tract cancer (Valle 2016):



[1] Special considerations:
- Need for pre-operative biliary drainage
- Avoid percutaneous biopsy in resectable disease
- Assess Future Liver Remnant
- Assess need for Portal Vein Embolisation
- Neoadjuvant approach (selected cases)
- Completion surgery for incidental gallbladder cancer of T-stage T1b and above

[2] Option of salvage surgery should be considered in responding patients with initially inoperable disease
[3] Level of recommendation IV,C
[4] Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

For patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement Pemazyre (Pemigatinib) was approved and is available in the EU in 2021.

5.1.3. Main clinical studies

This conditional marketing application is based on the results observed in Cohort 1 in the phase 2 single-arm trial (SAT) CBGJ398X22204 *("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*"). This means in the second-line treatment setting and beyond of locally advanced or metastatic cholangiocarcinoma (CCA) with FGFR2 fusion or rearrangement.

This trial was a multiply analysed, fundamentally amended, uncontrolled, open-label explorative study started with inclusion of the first subject on 23 July 2014. Date of data cutoff (after two interim-analyses) was 01 March 2021.

At study entry, 99.1% of subjects had stage IV cancer (including 68.5% with lung metastases and 25.9% with bone metastases), and 96.3% of subjects had progressed on ≥1 prior regimen. 53.7% of subjects were heavily pretreated and received infigratinib as third- or later-line therapy. All but 1 subject received prior gemcitabine-based therapy, and most (88.0%) had progressed on their prior gemcitabine-based therapy.

Participants were assigned to cohorts based on tumour FGF/FGFR status. FGFR2 fusions and other rearrangements were identified using a variety of local tests (89%) or a centralised clinical trial assay (11%). In the presented analysis Cohort 1 included only participants with FGFR2 rearrangement or fusion.

The primary endpoint of efficacy of the study is the ORR assessed by BICR in participants of the Cohort 1 accompanied by secondary endpoints. ORR is supported by Best Overall Response (BOR), duration of response (DOR) PFS and OS as secondary endpoints all assessed by BICR. In addition, investigator's assessment regarding the outcome for the same endpoints was submitted.

5.2. Favourable effects

Outcome assessed by blinded independent central review (BICR)

The primary efficacy endpoint of ORR (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.was 23.1% (95% CI: 15.6, 32.2) among subjects with FGFR2 fusion/rearrangement in Cohort 1 FAS with a median DOR of 5.55 months (95% CI: 3.78, 7.66).

1/108 subject had confirmed CR by BICR (0.9%)

24/108 subjects had confirmed PR by BICR (22.2%)

Of the 25 subjects who achieved a confirmed CR or confirmed PR by BICR, 9 subjects (36.0%) had a response duration ≥6 months.

BOR assessed by BICR was confirmed 1/108 CR (0.9%), confirmed 24/108 PR (22.2%), confirmed 66/108 with stable disease (61.1%), and 11/108 with progressive disease (10.2%). The BOR outcome in the remaining subjects (15.8%) was reported as "unconfirmed" and progressive disease or "not done".

5.3. Uncertainties and limitations about favourable effects

Overall, exposure-response analyses did not indicate any significant relationship for efficacy measures of PFS or OR and exposure, neither for infigratinib or its metabolites alone nor for overall AUC activity, which included the activity of the metabolites.

PK parameters of infigratinib and its active metabolites BHS697, CQM157 and BQR917 are unsatisfactorily investigated. The weaknesses concern, at least, the bioanalytical methods with too high LLOQ, unsatisfactory quality of the mass balance study, 5 different formulations for a BCS IV drug substance of which the final to-be-marketed FMI IV has unclear bioequivalence and food-effect, large variability at least due to auto-inhibition of the main metabolising pathway via CYP3A4, evaluation of the primary and secondary PK parameters for at least 2 of 3 active metabolites in all relevant studies, design of the dedicated RI and HI studies, and finally, dose finding based on MTD and "dose interruption observations" for a targeted drug substance without a pre-defined proof-of-concept of a potential efficacious exposure.

Key DDI studies were performed, however the effect sizes of single-dose infigratinib may not be fully representative for and extrapolatable to steady-state drug treatment.

There are general methodological shortcomings in the clinical pharmacokinetics/pharmacology development, including at least different formulations with formulation- and compound-immanent PK factors like pronounced food-effect, enormous variability in exposure that was lower e.g. at 60 mg vs. 125 mg in the dose finding study and concentration-dependent autoinhibition of the main metabolising pathway, without any E-R relationship for efficacy but for safety.

All analyses of the pivotal study CBGJ398X22204 need to be considered exploratory as the efficacy results claimed are based on post-hoc selection of subpopulations from a single multiply analysed, fundamentally amended, uncontrolled, open-label study.

The size of the effects on ORR 23.1% (95% CI 15.6, 32.2) and median DOR 5.55 months (95% CI 0.92, 19.12) is not such that it is reasonable to assume clinically relevant effects on PFS, OS or HRQoL and exclude a major detriment in any of these effects.

In the absence of a randomised comparator the impact of the treatment with infigratinib on PFS and OS cannot be reliably estimated. In particular, the impact on PFS and OS cannot be disentangled from prognostic factors, which is particularly relevant in this context where it is not clear yet whether FGFR2 fusions/rearrangement is a positive prognostic factor.

In addition, it seems that even the rules for dose reductions as listed in the SmPC were not pre-specified in the protocol and reliablitiy of these recommendations may be challenged. The applicant needs to compare the inhibition of the FGFR2 needed for efficacy according to the blood levels yield with the proposed dose reductions steps in order to assess whether a sufficient efficacy can be expected after dose reduction and to reject the hypothesis that a lower dose should be used. In particular, since it seems that for the confirmative trial for the CMA the same posology is used and similar dose reductions can be foreseen.

Information regarding the identified FGF/FGFR Genetic Alterations Identified by local or central Genomics Laboratory in the study population at the time of inclusion as well as whether other concomitant genetic alterations beside the target mutation were also identified remains missing yet need clarification. Also detailed information on the analytical performance (including assay platform, specimen, pre-analytical sample processing requirements and read-out) and validity of assays has not been submitted however, should be provided. As regards analytical validity, the suitability of assays used should be demonstrated (e.g. robustness, accuracy, specificity, sensitivity and linearity, as appropriate for method). It should also be indicated if tumour heterogeneity is relevant in case of cholangiocarcinoma with FGFR2 fusion or rearrangement and if/how this has been addressed during analytical assay validation.

The confirmative phase III trial QBGJ398-301 in order to fulfil the condition for the applied CMA has enrolled the first subject on 27 Dec 2019. In order to assess the feasibility of the proposed time-frame for this trial, the applicant is requested to report the current number of patients already included since 2019.

5.4. Unfavourable effects

Safety assessment in this application and the applied indication has to focus on the primary safety data set of 108 subjects with an FGFR2 gene fusion or rearrangement in CBGJ398X2204 Cohort 1, who received at least 1 dose of study drug by the analysis cut-off date of 01 March 2021.

Additional safety analysis is provided from a larger population of 363 subjects who received infigratinib 125 mg QD on a 3 weeks on and 1 week off dosing schedule in trial CBGJ398X2101 (115 subjects with advanced solid malignancies), trial CBGJ398X2201 (26 subjects with glioblastoma), pivotal trial CBGJ398X2204 (All Cohorts 1-3; 108+30), and trial CBGJ398XUS04 (84 subjects with advanced solid or haematological malignancies). However, since exposure in this larger, but very heterogeneous data set was significantly shorter (Median 2.79 months versus 5.59 in the target population), the reliability of this outcome for the applied population seems rather uncertain. Although analysis of differences between both populations is missing, in general outcome is rather similar. This can be expected, since about one third of the included population (n=108/363) reflects the pivotal primary safety population. Moreover, the longer exposure in the 108 patients from the pivotal trial, indicate that exposure in the additional 255 patients must have been very short.

Median duration of exposure to infigratinib was 5.59 months; 13.0% of subjects were exposed for >12 months. Median relative dose intensity was 77.6%.

At least 1 AE was observed in 99.1% of subjects had at least 1 AE.

The most common preferred terms (PTs) were hyperphosphataemia (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%).

65.7% of subjects had at least 1 Grade 3 or Grade 4 AE (combined), 56.5% had at least 1 Grade 3 AE, and 9.3% had at least 1 Grade 4 AE. Most of the Grade 3 or Grade 4 AEs were due to abnormal laboratory findings and included stomatitis (14.8%), hyponatraemia (13.0%), and hypophosphataemia (13.0%).

32.4% of subjects had at least 1 treatment-emergent SAE, and 8.3% had an investigator-assessed treatment-related SAE. The most common SAEs were anaemia (3.7%), pyrexia (3.7%), hypercalcaemia (3.7%), and sepsis (2.8%).

89 subjects (82.4%) died during the study: 80 (74.1%) due to the study indication and 9 (8.3%) due to other causes. Six deaths occurred during the on-treatment period, each due to the study indication. A seventh subject had an on-treatment AE with a fatal outcome (Grade 4 sepsis, not related to study treatment); this death was not captured as on-treatment.

19.4% of subjects discontinued study drug due to an AE (based on the AE eCRF). No AE led to treatment discontinuation in >2 subjects.

65.7% of subjects had an AE that led to a dose interruption, 61.1% had a dose adjustment due to an AE, and 95.4% required concomitant medication or non-drug therapy due to an AE.

Incidence of AEs of special interest (AESIs) were as follows: calcium phosphate homeostasis (85.2%); eye disorder, including CSR/RPED (70.4%); CSR/RPED (16.7%); cardiac disorder (22.2%); tissue calcification (3.7%); acute pancreatitis (narrow) (0.9%); pathological fracture (0.9%); and vascular calcification/mineralisation (0.9%).

77.8% of subjects had hyperphosphataemia, which was Grade 3 in 12.0% (there were no Grade 4 events). Hyperphosphataemia was the most common AE that led to dose interruption or dose adjustment. At least 80.6% of subjects took a phosphate-binding medication. Onset of hyperphosphataemia occurred at a median of 8 days (range: 1-78 days) and resolved in most subjects.

Hypophosphataemia and hypercalcaemia occurred in 23.1% and 26.9% of subjects, respectively, and were mostly Grade 1 or 2 in severity; 3 Grade 4 events were observed in 2 subjects. No subjects discontinued study drug due to these events.

Serous retinal detachment events cursed with an accumulation of fluid in subretinal space probably because of an altered homeostasis. Significant loss of vision may be the consequence leading to blinding in the worst case. 70.4% of subjects had an eye disorder, including CSR/RPED (counted as an AESI), and 16.7% had CSR/RPED alone. The most common eye disorders were dry eye (36.1%) and blurred vision (21.3%). Eye disorders were generally Grade 1 or 2 in severity; 1 was Grade 4 (cataract). Most events of CSR/RPED were Grade 1 or 2; 1 was Grade 3, and none were Grade 4. However, it needs to be considered that this AE may progress even after discontinuation of treatment. AESI of eye disorder led to dose interruption in 11.1% of subjects, dose adjustment in 7.4%, and use of concomitant medication or non-drug therapy in 44.4%. Relatively few subjects (≤3.7%) had a dose interruption, dose adjustment, or used a concomitant medication or non-drug therapy due to adverse events.

5.5. Uncertainties and limitations about unfavourable effects

Treatment in the pivotal study was recommended with infigratinib tablets at a dose of 125 mg (one 100 mg capsule and one 25 mg capsule), taken once daily for 21 days followed by 7 days off therapy. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. However, the presented data indicate that only a small proportion of subjects could be treated with the applied 125 mg dose as proposed in the posology. It seems that most subjects need toxicity-driven sustainable dose reductions shortly after start of treatment and were not able to return to the 125 mg dose. Thus, the applied posology in general seems pre-mature, not sufficiently justified and hardly tolerable in the target population. Serous retinal detachment events cursed with an accumulation of fluid in subretinal space probably as a consequence of an altered homeostasis. Significant loss of vision may be the consequence leading to blinding in the worst case. However, the severity of the risk as reported seemed to have been underestimated and there is not enough information related to the outcome, recurrence, management strategy or the effectiveness of the preventive measures proposed for these events. Additional ocular events have also been reported at relatively high frequency.

In total, 13 subjects as potential cases of drug-induced liver injury according Hy's Law were identified during clinical development. Each of these cases is reported to be confounded and may have had alternative aetiologies. Since the provided information regarding this issue is not fully comprehensible, the applicant needs to provide and discuss the relevant details regarding the potential Hy's law cases and to justify the conclusion in each case.

The risk of pathological fracture as observed in 9 subjects can be assessed as unsupported by the current clinical data, but remaining uncertainties need to be resolved. Since infigratinib leads to a significant dysregulation of the calcium-phosphate homeostasis, this issue as well as the impact of infigratinib on Vitamin D and parathyroid hormone needs clarification.

Infigratinib has the potential to cause ectopic tissue calcification that could lead to serious complications during 6 months of treatment as illustrated by the 4 subjects with tissue calcification reported from Study CBGJ398X2204. More information is needed whether and how the adverse events of special interest "tissue calcification" and "vascular" and intravascular mineralisation" were investigated or assessed in the trial to assess this outcome is reliable.

Nail toxicity, a well-known toxicity for FGFR2 inhibitors, is not adequately addressed in the safety documents and need to be assessed.

Considering that infigratinib has a lot of drug-drug interactions, but the severely ill cancer population is in need for potentially drug-interacting products, an analysis of the impact of the different DDI on needed concomitant medication in the target population is missing in order to identify potentially needed conflicting concomitant medications. A more detailed analysis of the concomitant medications administered during the trial is requested.

5.6. Effects Table

Effect	Short Description	Unit	Infigratinib	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR (BICR)	Cohort 1	N (%) (95% CI)	25 (23.1) (15.6, 32.2)	N/A		CSR CBGJ398 X22204
BOR (BICR)	Confirmed CR Confirmed PR Stable disease	N (%) N (%) N (%)	1 (0.9) 24 (22.2) 66 (61.1)			CSR CBGJ398 X22204
Median DOR	Cohort 1	Months (95% CI)	5.55 (3.78, 7.66)	N/A		CSR CBGJ398 X22204
Median PFS	Cohort 1	Months (95% CI)	7.29 (5.59, 7.56)	N/A		CSR CBGJ398 X22204
DCR	Cohort 1	N (%) (95% CI)	91 (84.3) (76.0, 90.6)	N/A		CSR CBGJ398 X22204
Median OS	Cohort 1	Months (95% CI)	11.86 (10.68, 14.85)	N/A		CSR CBGJ398 X22204
Unfavourable Effects[a]						
TEAEs	regardless causality	%	99.1	N/A		CSR CBGJ398 X22204
TEAEs Grade ≥ 3	regardless causality	%	65.7	N/A		CSR CBGJ398 X22204
Serious AEs	regardless causality	%	32.4	N/A		CSR CBGJ398 X22204
TEAEs leading to discontinuation	regardless causality	%	19.4	N/A		CSR CBGJ398 X22204
TEAEs leading to reduction	regardless causality	%	65.7	N/A		CSR CBGJ398 X22204
TEAEs leading to interruption	regardless causality	%	42.5	N/A		CSR CBGJ398 X22204
TEAEs leading to death	regardless causality	%	?	N/A		CSR CBGJ398 X22204

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Efficacy claims for infigratinib monotherapy in the treatment of "adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement" are based on one pivotal study CBGJ398X22204. All analyses of this study need to be considered exploratory as results are based on post-hoc selection of subpopulations from a multiply analysed, fundamentally amended, uncontrolled, open-label study.

The magnitude of the observed anti-tumour activity (ORR 23.1% [95% CI 15.6, 32.2], median DOR 5.55 months [95% CI 0.92, 19.12] is not deemed "outstanding and clinically meaningful"; i.e. not such that it is reasonable to assume clinically relevant effects on PFS, OS or HRQoL and exclude a major detriment in any of these effects.

In the absence of a randomised comparator the impact of the treatment with infigratinib on PFS and OS cannot be reliably estimated. In particular, the impact on PFS and OS cannot be disentangled from prognostic factors, which is particularly relevant in this context where it is not clear yet whether FGFR2 fusions/rearrangement is a positive prognostic factor.

The safety database in the claimed indication is considered limited. Based on available data, the toxicity profile of pemigatinib in adult patients is considered non-negligible. The characterisation of the safety profile in the applied posology is also hampered due to the fact that in the pivotal study X2204 most CCA patients need toxicity-driven sustainable dose reductions shortly after start of treatment and were not able to return to the 125 mg dose (mean relative dose intensity was ~78%).

The general methodological shortcomings in the clinical pharmacokinetics/-pharmacology development, including at least different formulations with formulation- and compound-immanent PK factors like pronounced food-effect, enormous variability in exposure that was lower e.g. at 60 mg vs. 125 mg in the dose finding study and concentration-dependent autoinhibition of the main metabolising pathway, without any E-R relationship for efficacy but for safety, also need to be considered when balancing favourable and unfavourable effects.

5.7.2. Balance of benefits and risks

Considering the unconvincing anti-tumour activity, the severe safety profile and the complex pharmacokinetic profile (i.e. a high variability in exposure, the complex metabolic issues, including the concentration dependent auto-inhibition with a significant accumulation, and the on and off treatment periods), the balance of benefit and risks is considered to be negative.

5.7.3. Additional considerations on the benefit-risk balance

Based on EU regulatory guidance (EC No 507/2006), a request for a CMA may be granted for seriously debilitating or life-threatening diseases or medicinal products to be used in emergency situations or for orphan medicinal products, where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required.

<u>All the following requirements need to be met:</u>

a. the benefit risk balance of the product is positive;
b. it is likely that the applicant will be able to provide comprehensive data;
c. the unmet medical needs will be fulfilled;

d. the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.

a.) As stated above, the benefit risk balance of infigratinib in the applied indication is not considered reliably positive.

b.) The applicant is proposing confirmatory data from a phase 3 RCT Study QBGJ398-301 (PROOF Trial) with gemcitabine plus cisplatin in the control arm in the first-line setting of previously untreated cholangiocarcinoma patients with FGFR2 fusions/rearrangements. The applicant stated that the first patient was included on 27 Dec 2019 and analysis for the primary outcome is expected for 2027. However, no information regarding the overall recruitment during the last 2 years was given. This is essential for answering the question whether it is likely that the applicant will be able to provide comprehensive data.

c.) In the same setting requested by the applicant, Pemazyre® (pemagatinib) recently received a conditional marketing approval in EU. According to EMA/CHMP/509951/2006, Rev.1, *"for the demonstration of fulfilment of unmet medical needs by a second or subsequent product, the accumulated clinical data and residual uncertainties concerning the effects of an already conditionally authorised medicine(s) should be taken into account. While the specific obligations are not yet fully completed, it is not possible to confirm the full benefit of a conditionally authorised product, therefore another medicinal product could potentially address the same unmet medical needs, provided it is expected, based on appropriate scientific data, that such a product addresses the unmet medical needs to a similar or greater extent than what is understood for the already conditionally authorised product."*. In the CMA justification, the applicant argues that inferior outcome in terms of ORR and DoR compared to pemagatinib might be explained by a difference in the included population, with inclusion of more advanced disease stage in the investigated infigratinib trial X2204 than in the pivotal FIGHT 202 trial for pemigatinib, this remains an unproven hypothesis.

d.) There is no convincing benefit to public health of the medicinal product's immediate availability on the market, which outweighs the risks due to need for further data.

5.8. Conclusion

The overall B/R of infigratinib in the intended indication and posology is considered negative.