



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Truseltiq

Active ingredients: Infigratinib

Sponsor: Adjutor Healthcare Pty Ltd

December 2022

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
AHCYL1	Adenosylhomocysteinase like 1
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC	Area under the concentration time curve
AUC ₀₋₂₄	Area under the concentration time curve over 24 hours
AUC _{0-inf}	Area under the concentration time curve from time zero extrapolated to infinity
BICC1	BicC family RNA binding protein 1
BICR	Blinded independent central review
BOR	Best overall response
C/F	Clearance
CCA	Cholangiocarcinoma
CCDC6	Coiled-coil domain containing 6
CI	Confidence interval
C _{max}	Maximum concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
DL	Dose level
DLP	Data lock point
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status

Abbreviation	Meaning
EU	European Union
FDA	Food and Drug Administration (United States of America)
FGFR	Fibroblast growth factor receptor
FGFR2	Fibroblast growth factor receptor 2
GLP	Good Laboratory Practice
IC ₅₀	Half maximal (50%) inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
mFOLFOX	Fluorouracil/leucovorin in combination with oxaliplatin
MTD	Maximum tolerated dose
OCE	Oncology Center of Excellence (Food and Drug Administration, United States of America)
OCT	Optical coherence tomography
PED	Pigment epithelial detachment
PFS	Progression free survival
PI	Product Information
PK	Pharmacokinetic(s)
RECIST	Response Evaluation Criteria in Solid Tumours
REMS	Risk evaluation and mitigation strategy
RMP	Risk management plan
RPED	Retinal pigment epithelial detachment
SAE	Serious adverse event
TACC3	Transforming acidic coiled-coil containing protein 3
TGA	Therapeutic Goods Administration
T _{max}	Time of maximum concentration
US(A)	United States (of America)

Product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Product name:</i>	Truseltiq
<i>Active ingredient:</i>	Infigratinib (as phosphate)
<i>Decision:</i>	Approved for provisional registration
<i>Date of decision:</i>	2 November 2021
<i>Date of entry onto ARTG:</i>	5 November 2021
<i>ARTG numbers:</i>	348760, 348761, 348762, 348763
▼ Black Triangle Scheme:	Yes As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
<i>Sponsor's name and address:</i>	Adjutor Healthcare Pty Ltd; ¹ 3 Grandview Avenue Point Cook VIC 3030
<i>Dose form</i>	Hard capsule
<i>Strength:</i>	25 mg, 100 mg, and 25 mg + 100 mg (composite pack)
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	25 mg hard capsule packs: 42, and 63 capsules 100 mg hard capsule pack: 21 capsules Composite pack: 21 x 25 mg capsules + 21 x 100 capsules
<i>Approved therapeutic use:</i>	<i>Truseltiq has provisional approval in Australia 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.</i> <i>The decision to approve this indication has been made on the basis of overall response rate and duration of response in a single arm trial. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.</i>

¹ Sponsorship of Truseltiq was transferred from Adjutor Healthcare Pty Ltd, to Juniper Biologics Pty Ltd post-approval of Truseltiq.

<i>Route of administration:</i>	Oral
<i>Dosage:</i>	<p>The recommended dose of Truseltiq is 125 mg (one 100 mg hard capsule and one 25 mg hard capsule) orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles. Continue treatment until disease progression or unacceptable toxicity.</p> <p>Truseltiq should be taken on an empty stomach at least 1 hour before or 2 hours after a meal, at approximately the same time each day (preferably in the morning). Swallow the hard capsules whole with a large glass of water. Do not open, crush, chew, or dissolve the hard capsules.</p> <p>If a dose of Truseltiq is missed by ≥ 4 hours or if vomiting occurs, resume the regular daily dose schedule for Truseltiq the next day.</p> <p>See Section 4.2 Recommended dosage modifications for adverse reactions of the Product Information for dosage information in adverse reactions including ocular disorders (central serous retinopathy/retinal pigment epithelial detachment), and hyperphosphataemia.</p> <p>See Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties for recommended dosage modifications in mild and moderate renal impairment, and moderate hepatic impairment.</p> <p>For further information regarding dosage, refer to the Product Information.</p>
<i>Pregnancy category:</i>	<p>D</p> <p>Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.</p> <p>The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.</p>

Product background

This AusPAR describes the submission by Adjutor healthcare Pty Ltd (the sponsor) to register Truseltiq (infigratinib) 25 mg and 100 mg hard capsules for the following proposed indication:

Truseltiq 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.

Cholangiocarcinoma (bile duct cancer) is a rare, heterogeneous malignancy that originates from the neoplastic transformation of cholangiocytes into intrahepatic, perihilar, or distal extrahepatic tumours.²

In Europe, United States of America (USA) and Australasia, the incidence of cholangiocarcinoma (CCA) is low (0.3 to 3.5 per 100,000);³ in parts of the world where liver fluke infection is common (for example, in Thailand, China and South Korea).^{4,5,6}

Cholangiocarcinoma is the second most common primary liver tumour worldwide after hepatocellular carcinoma.

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. 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, non-alcoholic fatty liver disease, and tobacco use.^{3,7}

The growing understanding of the genetic alterations involved in the tumorigenesis of cholangiocarcinoma provides new therapeutic options for molecular targets. Among other genetic alterations, recurrent gene fusions involving the fibroblast growth factor receptor (FGFRs) are an important class of driver mutations in a number of tumour types, including cholangiocarcinoma. Kinase domain intact FGFRs can form fusions with various fusion partners and exhibit constitutive activation of the kinase activity, suggesting that these may serve as potential therapeutic targets via kinase inhibition. Cancer types harbouring FGFR fusions are quite diverse. In addition to cholangiocarcinoma, FGFR2 fusions with different partners have been detected in bladder, thyroid, prostate, pancreatic, breast, lung, glioma, and other cancer types.

Fibroblast growth factor receptor 2 (FGFR2) fusions are the most common FGFR genetic aberrations in cholangiocarcinoma.⁸ FGFR2 fusions with different partners, such as BicC family RNA binding protein 1 (*BICC1*), transforming acidic coiled-coil containing protein 3 (*TACC3*), coiled-coil domain containing 6 (*CCDC6*), and adenosylhomocysteinase like-1 (*AHCYL1*), have been detected in approximately 13% to 17% of intrahepatic

² Alpini G, McGill JM, Larusso NF. The pathobiology of biliary epithelia. *Hepatology*. 2002;35(5):1256–1268.

³ Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol*. 2016; 13(5): 261- 280

⁴ Global Burden of Disease Cancer Collaboration. The global burden of cancer 2013. *JAMA Oncol*. 1, 505–527 (2015).

⁵ Cardinale V, et al. Intra-hepatic and extra-hepatic cholangiocarcinoma: new insight into epidemiology and risk factors. *World J. Gastrointest. Oncol*. 2, 407–416 (2010).

⁶ Bridgewater J, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J. Hepatol*. 60, 1268–1289 (2014).

⁷ Khan, Shahid A., Simona Tavorlari, and Giovanni Brandi. Cholangiocarcinoma: Epidemiology and risk factors. *Liver International* 39 (2019): 19-31.

⁸ Jain A, et al. Cholangiocarcinoma with FGFR genetic aberrations: a unique clinical phenotype. *JCO Precision Oncol*. 2018.

cholangiocarcinomas.^{9,10,11,12} 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 signalling pathway, resulting in uncontrolled cell proliferation, survival and migration, which are hallmarks of cancer.^{13,14} FGFR inhibition reduces cancer cell proliferation in vitro, decreases tumour growth in *in vivo* FGFR2 fusion-positive cholangiocarcinoma models, and has demonstrated single-agent 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 patients with cholangiocarcinoma.

Cholangiocarcinoma is a serious and life-threatening disease with very limited treatment options and an overall poor prognosis. The only chance for cure is surgical resection, for which only approximately one-third of patients are eligible.

Cisplatin/gemcitabine is the reference chemotherapy regimen¹⁵ for good Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 1;¹⁶ patients; oxaliplatin may be substituted for cisplatin where there is a concern about renal function standard of care first line treatment of advanced or metastatic cholangiocarcinoma has a median survival of < 1 year. Further supporting the lack of therapeutic options, the 5-year survival rate for patients with cholangiocarcinoma was reported to be less than 10%. For patients who have progressed after first line treatment, there are few therapeutic options and there remains a significant unmet need for new therapies.

For patients with advanced cholangiocarcinoma who relapse after first line therapy, a meta-analysis of available treatments supported a mean overall survival of 7.2 months with a mean progression-free survival of 3.2 months and mean response rate of 7.7%. The only standard of care second line option supported by randomised data is

⁹ Arai Y, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology*. 2014;59(4):1427–1434.

¹⁰ Jain A, et al. Genomic profiling of biliary tract cancers and implications for clinical practice. *Curr Treat Options Oncol*. 2016;17(11):58.

¹¹ Churi CR, et al. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One*. 2014;9(12):e115383.

¹² Graham RP, et al. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. *Hum Pathol*. 2014;45(8):1630–1638.

¹³ Touat M, et al. Targeting FGFR signaling in cancer. *Clin Cancer Res*. 2015;21(12):2684–2694.

¹⁴ Babina IS, Turner NC. Advances and challenges in targeting FGFR signaling in cancer. *Nat Rev Cancer*. 2017;17(5):318–332.

¹⁵ Valle J, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273–1281.

¹⁶ **ECOG Performance Status:** The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

- 0 - Fully active, able to carry on all pre-disease performance without restriction
- 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 - Dead

fluorouracil/leucovorin in combination with oxaliplatin (mFOLFOX) + active symptom control in Study ABC-06, with a response rate of 5% and median PFS of 4 months.¹⁷

In the ABC-06 trial, the most frequent Grade 3/4 adverse events reported in the mFOLFOX group included fatigue/lethargy (19%), biliary event (19%), infection (14%), and neutrophil count decreased (12%).¹⁷

The growing understanding of the genetic alterations involved in the tumorigenesis of cholangiocarcinoma provides new therapeutic options for molecular targets. Among other genetic alterations, recurrent gene fusions involving the FGFRs are an important class of driver mutations in a number of tumour types, including cholangiocarcinoma. Kinase domain intact FGFRs can form fusions with various fusion partners and exhibit constitutive activation of the kinase activity, suggesting that these may serve as potential therapeutic targets via kinase inhibition. FGFR2 fusions are the most common FGFR genetic aberrations in cholangiocarcinoma.¹⁸ FGFR2 fusions with different partners, such as BICC1, TACC3, CCDC6, and AHCYL1, have been detected in approximately 13% to 17% of intrahepatic cholangiocarcinomas.^{19,20,21}

Erdafitinib the first marketed tyrosine kinase inhibitor of FGFRs 1 to 4 in the USA, received accelerated approval by the United States (US) Food and Drug Administration (FDA) for the treatment of previously treated advanced urothelial carcinomas with selected FGFR genetic alterations in April 2019.

The US FDA granted accelerated approval of pemigatinib in April 2020 for the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement.

In this submission the sponsor has stated:

‘The recent first FDA accelerated approval of an fibroblast growth factor receptor (FGFR) inhibitor [that is, pemigatinib] for patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement substantiates the importance of FGFR2 fusions or rearrangements as a promising target for therapy in advanced cholangiocarcinoma.

Despite these advances, an urgent need remains for additional, less toxic, effective therapies.’

Neither erdafitinib nor pemigatinib have been approved for use in Australia.

This evaluation was facilitated through [Project Orbis](#), an initiative of the United States Food and Drug Administration (FDA) Oncology Center of Excellence (OCE). Under this project, the FDA, Health Canada and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of

¹⁷ Lamarca A, et al. ABC-06. A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. Paper presented at: *American Society of Clinical Oncology (ASCO) Annual Meeting*; May 31-June 4, 2019; Chicago, IL. Abstract #4003.

¹⁸ Jain A, et al. Genomic profiling of biliary tract cancers and implications for clinical practice. *Curr Treat Options Oncol*. 2016;17(11):58.

¹⁹ Graham RP, et al. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. *Hum Pathol*. 2014;45(8):1630–1638.

²⁰ Ross JS, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. *Oncologist*. 2014;19(3):235–242.

²¹ Farshidfar F, et al. Integrative genomic analysis of cholangiocarcinoma identifies distinct IDH-mutant molecular profiles. *Cell Rep*. 2017;18(11):2780–2794. Correction in: *Cell Rep*. 2017;19(13):2878–2880.

evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

This product received [orphan drug designation](#) on 30 October 2020 for the following indication:

The treatment of cholangiocarcinoma.

In the USA Truseltiq was granted accelerated approval by the US FDA on 28 May 2021 for the indication:

Truseltiq (infigratinib) is an FGFR tyrosine kinase inhibitor 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 as detected by an FDA-approved test.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA [PI/CMI search facility](#).

Registration timeline

The following table captures the key steps and dates for this submission.

Description	Date
Designation (Orphan)	30 October 2020
Determination (Provisional)	30 October 2020
Submission dossier accepted and first round evaluation commenced	4 January 2021
First round evaluation completed	3 June 2021
Sponsor provides responses on questions raised in first round evaluation	2 July 2021
Second round evaluation completed	24 August 2021
Delegate's Overall benefit-risk assessment	6 October 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	2 November 2021
Completion of administrative activities and registration on the ARTG	5 November 2021
Number of working days from submission dossier acceptance to registration decision*	189

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

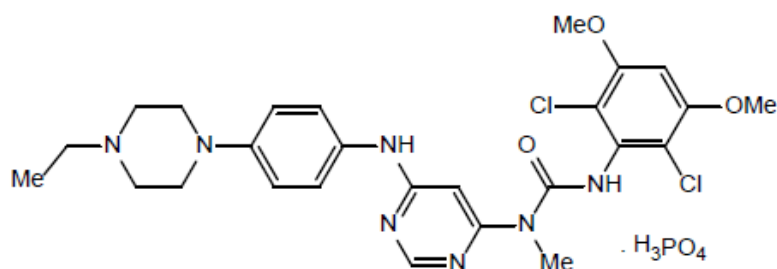
This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

Infigratinib is a tyrosine kinase inhibitor. Infigratinib is proposed to treat adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangements. The structure is achiral and includes an ethylpiperazine N-linked to a pyrimidine that is linked via a methylurea to a dichlorinated dimethoxyphenyl ring. It is a phosphate salt. Other tyrosine kinase inhibitors include

zanubrutinib and tucatinib. The skeletal structure of infigratinib is shown below in Figure 1.

Figure 1: Structure of infigratinib phosphate



Each Truseltiq 25 mg hard capsule contains 25 mg of infigratinib (as phosphate). Truseltiq 25 mg is a hard gelatin capsule having a white opaque body and grey opaque cap, with 'INFI 25mg' printed in black on the body of the capsule.

Each Truseltiq 100 mg hard capsule contains 100 mg of infigratinib (as phosphate). Truseltiq 100 mg is a hard gelatin capsule having a white opaque body and light orange opaque cap, with 'INFI 100mg' printed in black on the body of the capsule.

Each Truseltiq hard capsule contains the following inactive ingredients (excipients):

- Hard capsule content: lactose monohydrate, microcrystalline cellulose, crospovidone, hypromellose, magnesium stearate (from vegetable source), colloidal anhydrous silica.
- Hard capsule shell content: gelatin (bovine), titanium dioxide, iron oxide red (100 mg hard capsules only), iron oxide yellow (100 mg hard capsules only), iron oxide black (25 mg hard capsules only).

Truseltiq is supplied as multi-day PVC/PCTFE blister packs with aluminium foil lidding with the following configurations:

- Truseltiq 1 x 25 mg hard capsule and 1 x 100 mg capsule (125 mg daily dose)
 - Composite pack, contains 21 x 25 mg and 21 x 100 mg hard capsules.
- Truseltiq 1 x 100 mg hard capsule (100 mg daily dose)
 - Pack contains 21 x 100 mg hard capsules).
- Truseltiq 3 x 25 mg hard capsules (75 mg daily dose)
 - Pack 1: Weeks 1 and 2 contains 42 x 25 mg hard capsules.
 - Pack 2: Weeks 3 and 4 contains 21 x 25 mg hard capsules.
- Truseltiq 2 x 25 mg hard capsules (50 mg daily dose)
 - Pack contains 42 x 25 mg hard capsules.

Truseltiq has a shelf life of 28 months and should be store below 25°C.

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

The quality evaluator has no objection to registration from quality evaluation.

Nonclinical

The submitted nonclinical dossier was in accordance with the relevant International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for the nonclinical assessment of anticancer pharmaceuticals.²² The overall quality of the nonclinical dossier was high. All pivotal safety related studies were Good Laboratory Practice (GLP) compliant.²³

In vitro, infigratinib bound the FGFRs 1 to 3 receptors with nanomolar affinity. The major human metabolites, BHS697 and CQM157, bound the FGFRs 1 to 3 receptors with similar affinity to infigratinib. *In vivo*, infigratinib inhibited tumour growth in patient derived xenograft models of human cholangiocarcinoma driven by distinct FGFR2 fusions in a dose dependent manner. Consistent with the activity and selectivity of infigratinib against FGFR1 to 3 kinase targets, the animal studies support the proposed clinical indication.

No notable clinically relevant off target effects were noted for infigratinib, and major active metabolites of infigratinib (BHS697 and CQM157) in secondary pharmacodynamics screens.

Safety pharmacology studies did not reveal any significant effects on cardiovascular system of telemetered dogs or on central nervous system (CNS) and respiratory functions in rats. However, given the low exposures achieved, no firm conclusions can be drawn from the animal data regarding potential effects on CNS, cardiovascular or respiratory function in patients. *In vitro*, the human hERG channel data indicated a low potential for infigratinib to prolong the QT interval.²⁴

Plasma protein binding of infigratinib was high to very high in humans and all tested animal species. Infigratinib crossed the blood brain barrier in rats. Infigratinib and/or its metabolites accumulated in melanin containing tissues (eyes, meninges and skin of pigmented rats) and were eliminated from these tissues much slower than plasma/blood. Infigratinib was extensively metabolised in animals and humans. The two major human metabolites (BHS697 and CQM157) were also identified in rats and dogs. *In vitro* studies showed the cytochrome P450 (CYP) family enzyme CYP3A4;²⁵ as the major enzyme responsible for infigratinib metabolism with a minor contribution by the enzyme FMO3. Drug-related material was mainly excreted via faeces in humans and animal species. Biliary excretion of drug-related material was noted in rats and dogs. Overall, the pharmacokinetic profile in rats was sufficiently similar to that of humans. Due to the

²² EMA/CHMP/ICH/646107/2008, ICH S9 Non-clinical evaluation for anticancer pharmaceuticals.

²³ **Good Laboratory Practice (GLP)** is intended to promote the quality and validity of test data. It is a managerial concept covering the organisational process and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported (OECD GLP Guideline). Good Clinical Laboratory Practice (GCLP) applies those principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it ensures that the objectives of the GCP principles are carried out. This ensures the reliability and integrity of data generated by analytical laboratories.

²⁴ The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

²⁵ **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

species differences in metabolism, dogs were considered a less suitable animal model for safety assessments.

Strong and moderate CYP3A inhibitors/inducers are expected to significantly alter the systemic exposure to infigratinib. In vitro, infigratinib was shown to be a substrate of P-glycoprotein and BCRP efflux transporters. Strong and moderate P-glycoprotein and/or BCRP inducers/inhibitors may alter the absorption of infigratinib and thus its clinical exposure. Infigratinib is expected to increase the exposure of co-administered drugs that are substrates of BCRP. Systemic drug interaction is possible via MATE1 at clinically relevant infigratinib exposure.

Limited, non-GLP acute oral toxicity studies in rats and dogs indicate low acute toxicity.

Repeat dose toxicity studies were appropriate in terms of animal numbers and study duration (up to 26 weeks in rats and 39 weeks in dogs). The main target organs/toxicity findings were mineralisation of soft tissues (probably secondary to changed calcium/phosphorus homeostasis), bone (growth plate thickening, decreases in bone strength and density), eye (cornea opacity), hair/skin (hyperkeratosis and long hair) and liver (centrilobular vacuolation and mild focal necrosis). Most of these effects subsided at the end of recovery period with the exception of incisor teeth, hair coat changes, and ectopic tissue mineralisation (partially reversible at some dose levels/dosing durations). Most of these effects are consistent with the pharmacological actions of infigratinib. Considering the subclinical exposure of infigratinib (and/or its metabolites) at all dose levels, all these toxic effects are expected in patients.

Infigratinib was found to be neither mutagenic nor clastogenic. The absence of carcinogenicity study with infigratinib was acceptable given the indication in advanced cancer. Based on in silico analysis, the major metabolite BHS697 did not exhibit bacterial mutagenicity potential whereas the prediction of bacterial mutagenicity potential of metabolite CQM157 was inconclusive. A follow up screening study indicated metabolite CQM157 was not genotoxic; however, the study was inadequate. An appropriate mutagenicity study with metabolite CQM157 should be conducted as a post-marketing commitment.

Fertility was unaffected in male and female rats at subclinical exposures to infigratinib. Infigratinib was embryotoxic and teratogenic in rats and reduced ossification sites and fetal weights at subclinical exposures. Adverse fetal findings observed in the embryofetal development studies in both rats and rabbits are expected in patients considering subclinical exposure to infigratinib at all doses.

Pregnancy Category D is considered appropriate. Infigratinib should be contraindicated during pregnancy.

Infigratinib was not phototoxic *in vitro* and is not expected to exhibit phototoxic effects on patients.

Infigratinib was not a skin irritant and only caused mild eye irritation in rabbits.

Conclusions

The primary pharmacology studies support the proposed clinical indication.

The following toxic effects observed in nonclinical studies are expected in patients:

- Perturbation to calcium/phosphorus homeostasis and tissue mineralisation
- Bone (and/or teeth) toxicity
- Ocular toxicity
- Reproductive toxicity

Pregnancy category D is recommended.²⁶ Infigratinib should not be used during pregnancy.

An appropriate mutagenicity study with metabolite CQM157 should be conducted as a post-marketing commitment.

The nonclinical evaluator has no objection to registration from nonclinical evaluation.

Clinical

Mechanism of Action

Infigratinib is a small molecule kinase inhibitor of FGFR with inhibitory concentration, 50% (IC₅₀) values of 1.1, 1, 2, and 61 nM for FGFR1, FGFR2, FGFR3, and FGFR4, respectively. The major human metabolites of infigratinib, BHS697 and CQM157, have similar *in vitro* binding affinities for FGFR1, FGFR2, and FGFR3 compared to infigratinib. Infigratinib inhibited FGFR signalling and decreased cell proliferation in cancer cell lines with activating FGFR amplifications, mutations, or fusions. Constitutive FGFR signalling can support the proliferation and survival of malignant cells. Infigratinib had anti-tumour activity in mouse and rat xenograft models of human tumours with activating FGFR2 or FGFR3 alterations, including two patient-derived xenograft models of cholangiocarcinoma that expressed FGFR2-TTC28 or FGFR2-TRA2B fusions. Infigratinib demonstrated brain-to-plasma concentration ratios (based on area under the concentration time curve from time zero to infinity (AUC_{0-inf})) of 0.682 in rats after a single oral dose.

Pharmacodynamics

Truseltiq increased serum phosphate levels due to FGFR inhibition. Serum phosphate increased with increasing exposures across the dose range of 20 to 150 mg once daily (0.16 to 1.2 times the approved recommended dosage), with increased risk of hyperphosphatemia with higher exposure to Truseltiq.

Cardiac electrophysiology

At the recommended dosing regimen, Truseltiq does not result in a large mean increase (that is > 20 msec) in the QTc interval.²⁷ The QT effect of infigratinib at higher exposures associated with CYP3A inhibition has not been studied.

Pharmacokinetics

The infigratinib pharmacokinetic parameters are presented following administration of the approved recommended dosage in cholangiocarcinoma patients, unless otherwise specified.

The mean (coefficient of variation (%CV)) steady-state maximum concentration (C_{max}) and area under the curve over a dosing interval (area under the concentration time curve over 24 hours (AUC_{0-24h})) of infigratinib and active metabolites, BHS697 and CQM157, are presented in Table 1.

²⁶ **Australian Pregnancy Category D:** Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

²⁷ The **corrected QT interval (QTc)** estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

Table 1: Mean (%CV) exposure of infigratinib and active metabolites

	Infigratinib	BHS697	CQM157
C_{max}	282.5 ng/mL (54%)	42.1 ng/mL (65%)	15.7 ng/mL (92%)
AUC _{0-24h}	3780 ng•h/mL (59%)	717 ng•h/mL (55%)	428 ng•h/mL (72%)

Infigratinib C_{max} and area under concentration time curve (AUC) increased more than proportionally across the dose range of 5 to 150 mg (0.04 to 1.2 times the approved recommended dose). Steady state was achieved within 15 days and the mean accumulation ratio was 8- and 5-fold for C_{max} and AUC, respectively.

Absorption

Median (range) time to achieve peak infigratinib plasma concentration (t_{max}) was 6 hours (2 to 7 hours) at steady state.

Effect of Food

Following administration of Truseltiq with a high fat and high calorie meal (800 to 1000 calories with approximately 50% of total caloric content of the meal from fat) in healthy subjects, the mean area under concentration time curve extrapolated to infinity (AUC_{inf}) of infigratinib increased by 80% to 120% and C_{max} increased by 60% to 80%, the median time of maximum concentration (T_{max}) shifted from 4 hours to 6 hours. Following administration of Truseltiq with a low fat low calorie meal (approximately 330 calories with 20% of total caloric content of the meal from fat), the mean AUC_{inf} of infigratinib increased by 70%, C_{max} increased by 90%, and the median T_{max} did not change.

Distribution

The geometric mean (CV%) apparent volume of distribution of infigratinib was 1600 L (33%) at steady state. The mean infigratinib protein binding was 96.8%, primarily to lipoprotein, and was dependent of drug concentration.

Elimination

The geometric mean (CV%) total apparent clearance (CL/F) of infigratinib was 33.1 L/h (59%) at steady state. The geometric mean (CV%) terminal half-life of infigratinib was 33.5 h (39%) at steady state.

Metabolism

Infigratinib is predominantly metabolized by CYP3A4 (about 94%) and to a lesser extent by FMO3 (6%) *in vitro*. The major drug related moiety in plasma was unchanged infigratinib (38% of dose) in a human [14C] mass balance study, followed by two active metabolites, BHS697 and CQM157 (each at > 10% of dose). The metabolite BHS697 is mainly metabolised by CYP3A4 and the metabolite CQM157 is metabolised through both Phase I and Phase II biotransformation pathways.

The metabolites BHS697 and CQM157 contribute about 16% to 33% and 9% to 12% of overall pharmacologic activity, respectively.

Excretion

After a single oral 125 mg dose of radio-labelled infigratinib in healthy subjects, approximately 77% of the dose was recovered in faeces (3.4% as unchanged) and 7.2% in urine (1.9% as unchanged).

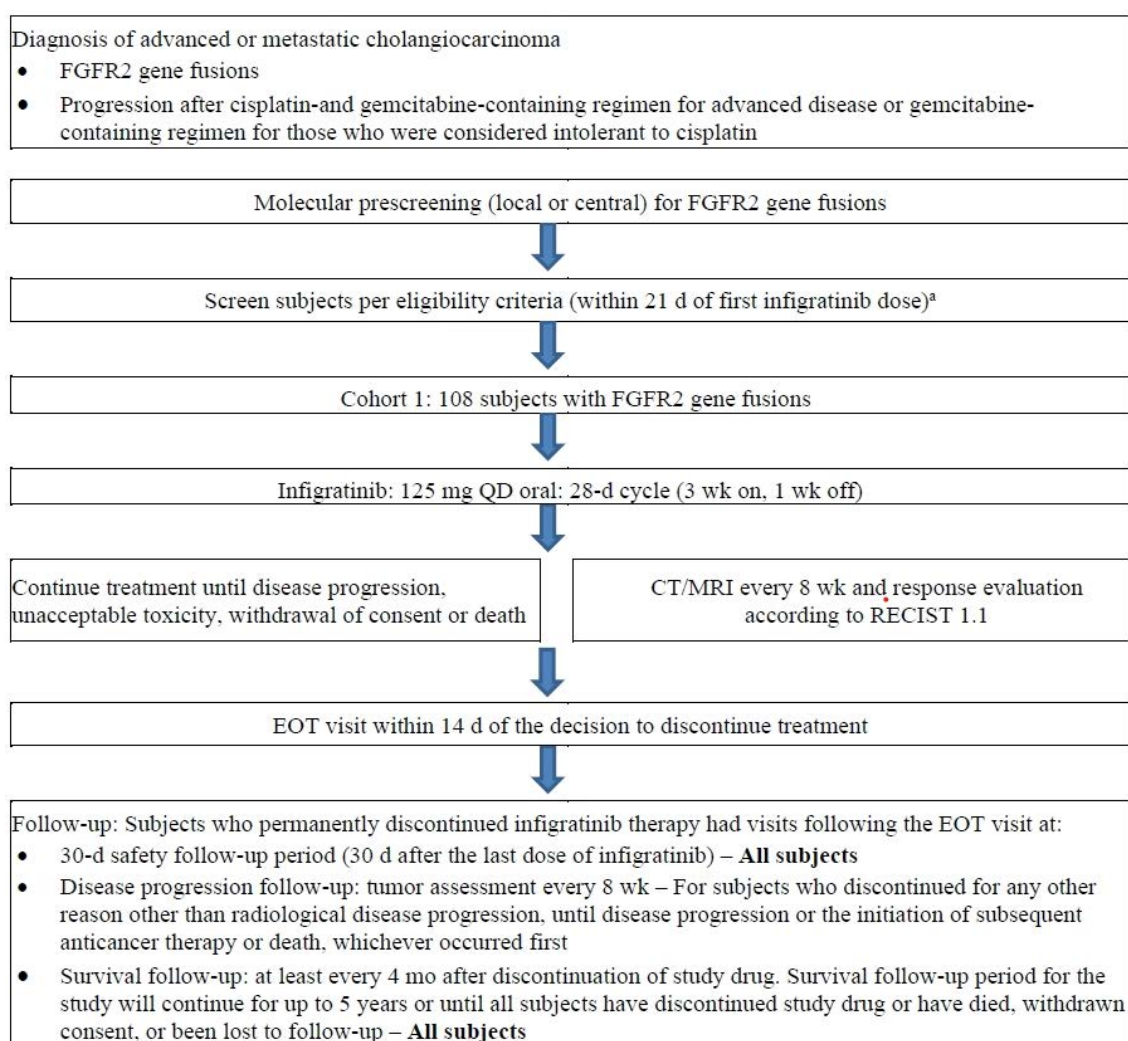
Study CBGJ398X2204***Study design***

Study CBGJ398X2204 in patients with cholangiocarcinoma who had FGFR2 gene fusions/rearrangements forms the basis of the primary analyses of safety and efficacy for this submission. This study has been published.²⁸

Study CBGJ398X2204 is an ongoing multicentre, open label, three cohort, Phase II study evaluating infigratinib anti-tumour activity in subjects with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations (enrolled in Cohort 1). Eligible study participants were required to have documented evidence of FGFR gene alterations determined through molecular pre-screening.

Eligible study participants were also required to have received at least one prior treatment regimen containing gemcitabine with or without cisplatin for advanced/metastatic disease. Subjects had to have evidence of progressive disease following their prior regimen, or if prior treatment was discontinued due to toxicity, had to have continued evidence of measurable disease. Interim analysis set 2 for Cohort 1 is the primary efficacy analysis set for the data presented in this marketing application. The Interim analysis set 2 for Cohort 1 includes subjects in Cohort 1 with FGFR2 gene fusions who received ≥ 1 dose of infigratinib. As of the data cutoff for this interim analysis, 108 subjects with FGFR2 gene fusions in Cohort 1 received at least one dose of study drug. An overview of study design is provided in Figure 3 below.

²⁸ Javle M, et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. *Lancet Gastroenterol Hepatol*. 2021;6(10):803-815.

Figure 2: Study CBGJ398X2204 design

Abbreviation: CT = computed tomography; d = day; EOT = end of treatment; FGFR2 = fibroblast growth factor receptor 2; mo = month; MRI = magnetic resonance imaging; QD = once daily; RECIST = Response evaluation criteria in solid tumours; wk = weeks

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

Subjects were enrolled across 18 study centres (nine centres in the USA, five in Western Europe, and four in Asia).

A control group was not included, given the lack of established therapy for this patient population.

Diagnostic Criteria includes histologically or cytologically confirmed cholangiocarcinoma.

Study CBGJ398X2204 includes adult subjects with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other FGFR genetic alterations who failed or were intolerant to gemcitabine-based antineoplastic treatment.

Main inclusion criteria include:

- Histologically or cytologically 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 gene fusions.
- Cohort 2: one of the following:
 - (a) FGFR1 fusions,
 - (b) FGFR3 fusions, or
 - (c) FGFR1/2/3 mutation known to be an activating mutation.
- Cohort 3: FGFR2 gene fusions (must receive prior treatment with an FGFR2 inhibitor).
- Evidence of measurable disease according to RECIST version 1.1.²⁹
- 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 performance status;¹⁶ ≤ 1 (subjects with an ECOG PS of 2 may be considered on a case-by-case basis after discussion with QEDTherapeutics).

The main exclusion criterion includes prior treatment with an FGFR inhibitor or MEK inhibitor is not allowed, with the exception of Cohort 3 (protocol amendment 4), which requires prior FGFR inhibitor therapy.

For dose selection, subjects received 125 mg once daily of infigratinib on a 3-week on (21 day)/1-week off (7 day) schedule in 28-day cycles. This regimen was selected based on safety and maximum tolerated dose (MTD), efficacy, and pharmacokinetics (PK) modelling during dose escalation during an early Phase I study (Study CBGJ398X2101), further evaluated in an expansion cohort in that study, and then used in this registrational study and other ongoing studies.

All subjects were assigned to receive oral infigratinib 125 mg once a day (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.

For patients who did not tolerate the protocol specified dosing schedule, dose adjustments were permitted in order to allow the patient to continue the study treatment. Each patient was to be allowed three dose reductions according to protocol-specified dose modifications for adverse events, with dose level reductions to three different reduced dose levels: the 100 mg dose level (DL -1), 75 mg (DL -2), and 50 mg (DL -3). Dose reductions to below 50 mg were not allowed. All dose modifications were to be based on the worst preceding toxicity. Following resolution of toxicity to baseline or Grade ≤ 1 , treatment was to be resumed at either the same or lower dose of study drug as per the criteria in the protocol. In addition, the study protocol included tabular dose reduction guidelines for management of mechanism-based toxicities, including hyperphosphatemia and ocular toxicity.

²⁹ The **Response Evaluation Criteria In Solid Tumours (RECIST)** is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

Efficacy endpoints

Primary study endpoints include overall response in Cohort 1 assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.²⁹ The estimated overall response rate is presented with corresponding 95% confidence interval (CI) based on the binomial distribution (Clopper-Pearson exact method) accompanied by duration of response to allow for more complete characterisation of the beneficial effect of infigratinib.

Secondary endpoints include:

- Overall response assessed by investigator; progression-free survival, best overall response (BOR), disease control assessed by investigator and by BICR according to RECIST 1.1; and overall survival (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 population).

Exploratory:

- Type, frequency, and severity of AEs and SAEs and tolerability (dose interruptions, reductions, and intensity) (Cohorts 2 and 3).
- Progression free survival, overall response, best overall response, response onset, and disease control assessed by the investigator per RECIST version 1.1, and overall survival (Cohorts 2 and 3)

Baseline and demographic characteristics

Subjects were enrolled in North America (71.3%), Western Europe (22.2%), or Asia (6.5%). Most subjects were white (72.2%) and most were female (62%). Mean age of the study population was 53.4 years (range: 23 to 81 years); 82 subjects (75.9%) were < 65 years of age.

All but one subject had a baseline ECOG PS of 0 (41.7%) or 1 (57.4%). The bile duct was the primary site of cancer in most subjects (98.1%). Nearly all (94.4%) of the subjects had non-liver metastatic disease at Baseline; the most common metastatic sites were the lung (68.5%) and lymph nodes (57.4%). Histological grade was typically characterised as moderately differentiated (38.9%), poorly differentiated (30.6%), unknown/missing (20.4%), or well differentiated (8.3%). At initial diagnosis, the most common cancer stage was Stage IV (70.4%).

Nearly all subjects had Stage IV disease at study entry (99.1%), with an FGFR2 fusion or other rearrangement, as determined in a local or central laboratory using next generation sequencing (89%) or other nucleic acid based tests (11%).

Median time from initial diagnosis to first infigratinib dose was 12.75 months (range: 1.74 to 152.94 months) and median time from the most recent recurrence/progression to first infigratinib dose was 1.4 months (range: 0.03 to 14.59 months). The majority of subjects (96.3%) had progressed on more than one prior regimen.

Overall, the demographics, baseline characteristics, and prior treatment of subjects enrolled in Study CBGJ398X2204 are representative of this refractory patient population and standard of treatment for cholangiocarcinoma. The predominantly younger and female population is also consistent with existing scientific literature describing patients with FGFR2 fusion positive cholangiocarcinoma.

Primary efficacy endpoint

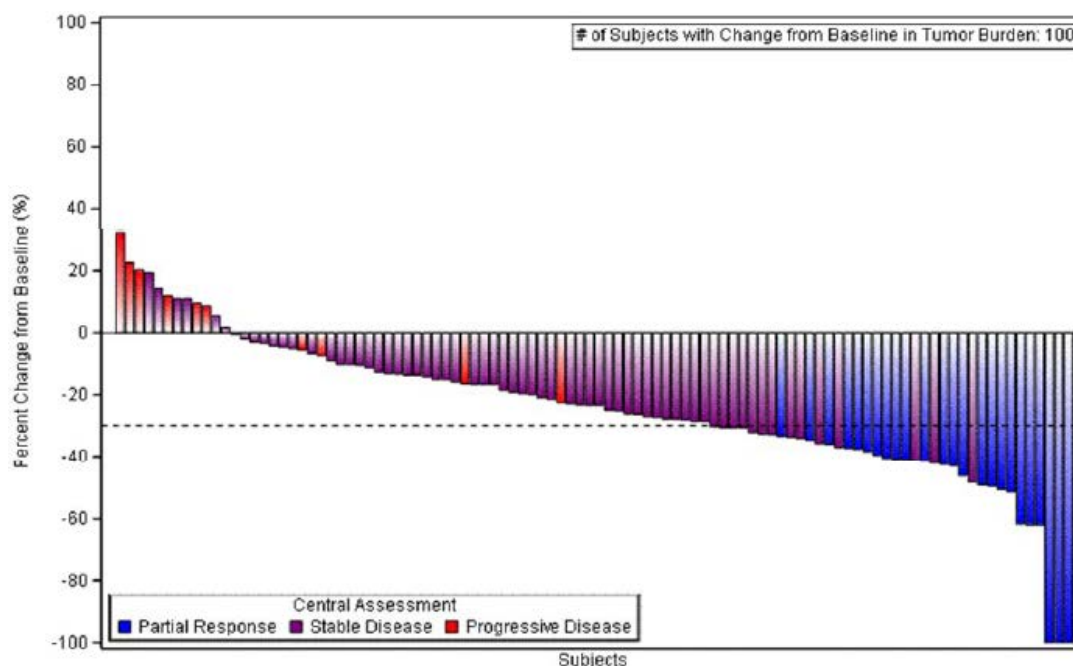
A summary of primary efficacy results for overall response rate assessed by BICR is presented in Table 2 below. According to BICR, the overall response rate was 23% (95% CI: 16%, 32%) with a median duration of response of 5 months (95% CI: 3.7, 9.3).

Table 2: Study CBGJ398X2204 Primary endpoint of overall response rate assessed by blinded independent central review

Efficacy Parameter	TRUSELTIQ N=108
	BICR Assessment
ORR (95% CI)	23% (16, 32)
Complete Response, n (%)	1 (1%)
Partial Response, n (%)	24 (22%)
Median DoR (months) (95% CI)	5.0 (3.7, 9.3)
Patients with DoR \geq 6 months, n (%)	8 (32%)
Patients with DoR \geq 12 months, n (%)	1 (4%)

Abbreviations: BICR = blinded independent central review; CI = confidence interval; DoR = duration of response; ORR = overall response rate.

Figure 3: Study CBGJ398X2204 Waterfall plot of maximum percent reduction in tumour burden with best response assessment by blinded independent central review (interim analysis set 2 for Cohort 1)



Abbreviation: BICR = blinded independent central review.

Note: The colour of the bars are based on confirmed response per blinded central assessment

Time to event endpoints like progression-free survival and overall survival are considered to be uninterpretable in a single-arm study. The analyses of progression free survival and overall survival in Study CBGJ398X2204 are considered exploratory and the results descriptive only.

Safety

Exposure

Study CBGJ398X2204

The primary safety analysis for this submission is based on the 108 patients from Cohort 1 of Study CBGJ398X2204 with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement.

Patients were treated orally with Truseltiq (infigratinib) 125 mg once daily for 2 consecutive days followed by 7 days off therapy, in 28-day cycles, until disease progression or unacceptable toxicity. The median duration of treatment (exposure) was 5.52 months (range: 0.03 to 28.29 months). The median age of Truseltiq (infigratinib) treated patients was 53 years (range: 23 to 81), 62% were females, and 72% were White.

89% of patients in Study CBGJ398X2204 discontinued treatment with infigratinib at the time of the primary analysis; 62% of patients discontinued treatment because of disease progression.

Other studies

An additional 243 patients with a variety of cancers treated with infigratinib as a single agent in 4 other multicentre single arm trials or cohorts of the Study CBGJ398X2204 provided additional, supportive safety data.

Although assessment of a causal relationship between infigratinib and treatment-emergent reactions was limited given the single arm design of the trials providing safety data, the adverse reactions observed in patients treated with infigratinib were largely expected given the mechanism of action and the toxicity profile observed in preclinical studies.

Adverse reactions

Study CBGJ398X2204

For Study CBGJ398X2204, adverse events were assessed by the investigator according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria and were coded using medical dictionary for regulatory activities version 21.0. Adverse events were assessed during the treatment period and for 30 days after the last dose of study drug.

Among the 108 patients with cholangiocarcinoma enrolled in Study CBGJ398X2204, the most common adverse reactions to infigratinib (occurring at an incidence rate $\geq 20\%$) are nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmar-plantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhoea, dry skin, decreased appetite, vision blurred and vomiting.

Table 3, shown below, has been extracted from the Australian PI summarising the adverse reactions in Study CBGJ398X2204.

Table 3: Study CBGJ398X2204 Adverse reactions (greater than or equal to 15%) in patients receiving Truseltiq (infigratinib) (N = 108)

Adverse Reaction	All Grades (%)	Grades $\geq 3^a$ (%)
Metabolism and nutrition disorders		
Hyperphosphataemia ^b	78	11
Hypercalcaemia	25	6
Hypophosphataemia	22	13
Decreased appetite	22	1
Skin and subcutaneous tissue disorders		
Nail toxicity ^c	57	2
Alopecia	38	0
Palmar-plantar erythrodysesthesia syndrome	33	7
Dry skin	23	0
Gastrointestinal disorders		
Stomatitis ^d	56	15
Constipation	30	1
Dry mouth	25	0
Diarrhoea	24	3
Vomiting	21	1
Nausea	19	1
Abdominal pain	17	4
Dyspepsia	17	0
Eye disorders		
Dry eye ^e	44	2
Eyelash changes ^f	25	0
Vision blurred	21	0
General disorders and administrative site conditions		

Adverse Reaction	All Grades (%)	Grades $\geq 3^a$ (%)
Fatigue ^g	44	4
Oedema ^h	17	1
Pyrexia	15	1
Musculoskeletal and connective tissue disorders		
Arthralgia	32	0
Pain in extremity	17	2
Nervous system disorders		
Dysgeusia	32	0
Headache	17	1
Investigations		
Blood creatinine increased	24	0
Aspartate aminotransferase increased	21	2
Weight decreased	15	2
Blood and lymphatic system disorders		
Anaemia	19	4
Respiratory, thoracic and mediastinal disorders		
Epistaxis	18	0
<p>Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03)</p> <p>a Events of Grade 3 only (no Grade 4 occurred) are marked with an asterisk</p> <p>b Includes ingrown nail, nail bed bleeding, nail bed disorder, nail bed inflammation, nail bed tenderness, nail discolouration, nail disorder, nail dystrophy, nail hypertrophy, nail infection, nail ridging, onychalgia, onychoclasia, onycholysis, onychomadesis, onychomycosis, and paronychia.</p> <p>c Includes mouth ulceration and stomatitis</p> <p>d Includes abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.</p> <p>e Severity of eye disorder is not represented by CTCAE grading</p> <p>f Includes dry eyes, keratitis, lacrimation increased, pinguecula, and punctate keratitis.</p> <p>g Includes blepharitis, eyelash changes, eyelash discolouration, growth of eyelashes, trichiasis, and trichomegaly.</p> <p>h Includes asthenia and fatigue</p> <p>i Includes edema peripheral and edema.</p>		

The most common laboratory abnormalities were increased creatinine, and calcium-phosphate analyte abnormalities.

Table 4, shown below, is an extract from the FDA prescribing information detailing select laboratory abnormalities with a worsening from Baseline in 10% or more patients.

Table 4: Study CBGJ398X2204 Select laboratory abnormalities (greater than or equal to 10%) worsening from Baseline in patients receiving TruselTiq (infigratinib)

Laboratory Abnormality	TRUSELTIQ N=108	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased hemoglobin	53	5
Decreased lymphocytes	43	9
Decreased platelets	37	4
Decreased leukocytes	26	3
Decreased neutrophils	14	2
Chemistry		
Increased creatinine	93	7
Increased phosphate ^a	90	13
Decreased phosphate	64	31
Increased alkaline phosphatase	54	8
Increased alanine aminotransferase	51	6
Increased lipase	44	7
Increased calcium	43	7
Decreased sodium	41	20
Increased triglycerides	38	3
Increased aspartate aminotransferase	38	4
Increased urate	37	37
Decreased albumin	24	1
Increased bilirubin	24	6
Decreased potassium	21	3
Increased cholesterol	18	1
Increased potassium	17	3
Decreased calcium	10	2

The denominator used to calculate the rate varied from 104 to 107 based on the number of patients with a baseline value and at least one post treatment value. These laboratory abnormalities are values that reflect worsening from Baseline.

Graded per NCI CTCAE version 4.03.

a NCI CTCAE version 4.03 does not define grades for increased phosphate. Laboratory value shift table categories were used to assess increased phosphorus levels (Grade \geq 3 defined as \geq 9 mg/dL)

US Prescribing Information

The following is an extract taken from the FDA-approved US prescribing information:

‘The most common (\geq 20%) adverse reactions were nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmar-plantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, vision blurred and vomiting. The most common laboratory abnormalities (\geq 20%) were increased creatinine, increased phosphate, decreased phosphate, increased alkaline phosphatase, decreased haemoglobin, increased alanine aminotransferase, increased lipase, increased calcium, decreased lymphocytes, decreased sodium, increased triglycerides, increased aspartate aminotransferase, increased urate, decreased platelets, decreased leukocytes, decreased albumin, increased bilirubin and decreased potassium.’

Serious adverse reactions

Serious adverse reactions occurred in 32% of patients receiving infigratinib. Serious adverse reactions in $\geq 2\%$ of patients who received infigratinib included infections, anaemia, pyrexia, abdominal pain, hypercalcaemia, and sepsis.

The following extract is taken from the FDA-approved US prescribing information:

‘Serious adverse reactions occurred in 32% of patients receiving Truseltiq. Serious adverse reactions in $\geq 2\%$ of patients who received Truseltiq included infections, anaemia, pyrexia, abdominal pain, hypercalcemia, and sepsis. Fatal adverse reactions occurred in 1 (0.9%) patient who received Truseltiq and was due to sepsis.’

The specific serious risks of ocular toxicity and hyperphosphataemia are discussed separately.

Events leading to discontinuation and dosage interruption

Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received infigratinib. Adverse reactions requiring permanent discontinuation (that is, adverse events related to treatment) in $\geq 1\%$ of patients were blood creatinine increased, fatigue, subretinal fluid and calcinosis.

Dosage reductions due to an adverse reaction occurred in 60% of patients who received infigratinib.

Adverse reactions requiring dosage reductions in $\geq 2\%$ of patients who received infigratinib included hyperphosphataemia, stomatitis, palmar-plantar erythrodysesthesia syndrome, increased blood creatinine, increased lipase, hypercalcaemia, and onycholysis.

Dosage interruptions due to an adverse reaction occurred in 64% of patients who received infigratinib. Adverse reactions requiring dosage interruption in $\geq 5\%$ of patients included hyperphosphataemia, hypercalcaemia, palmar-plantar erythrodysesthesia syndrome, stomatitis, diarrhoea and blood creatinine increased.

The following text is an extract from the FDA-approved US prescribing information:

‘Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received Truseltiq. Adverse reactions requiring permanent discontinuation in $\geq 1\%$ of patients were blood creatinine increased, fatigue, subretinal fluid, and calcinosis.

Dosage interruptions due to an adverse reaction occurred in 64% of patients who received Truseltiq. Adverse reactions requiring dosage interruption in $\geq 5\%$ of patients included hyperphosphatemia, hypercalcemia, palmar-plantar erythrodysesthesia syndrome, stomatitis, diarrhea, and blood creatinine increased.

Dosage reductions due to an adverse reaction occurred in 60% of patients who received TRUSELTIQ. Adverse reactions requiring dosage reductions in $\geq 2\%$ of patients who received Truseltiq included hyperphosphatemia, stomatitis, palmar-plantar erythrodysesthesia syndrome, increased blood creatinine, increased lipase, hypercalcemia, and onycholysis.’

Fatal events

Fatal adverse reactions (that is, fatal events related to treatment) occurred in 0.9% of patients and included sepsis.

The table below summarises the primary reasons for all deaths that occurred during the study. The on treatment period was defined as the period of time from the day of first dose to the day of last dose + 30 days (inclusive). The post-treatment period was defined as any time after the day of last dose + 30 days.

Table 5: Study CBGJ398X2204 Primary reasons for death (Interim analysis set 2 for Cohort 1)

Category	All Subjects (N=108) n (%)
Overall Death	70 (64.8)
Study Indication	62 (57.4)
Other	8 (7.4)
Death during the on-treatment period ^a	5 (4.6)
Study Indication	5 (4.6)
Death during the posttreatment period	65 (60.2)
Study Indication	57 (52.8)
Other	8 (7.4)

a A sixth subject had an on treatment TEAE with a fatal outcome (Grade 4 sepsis). The subject died 36 days after her last study treatment, so the death was not summarised here as on treatment, but the TEAE of sepsis that led to death started 7 days after the last study treatment. In the above table, this subject is included in the category 'Other' under 'Death during the post treatment period.'

Serious risks

Ocular effects: Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED)

Ocular toxicity is a serious risk of infigratinib (particularly retinal pigment epithelial detachment (RPED)). Given the lack of systematic optical coherence tomography (OCT) assessments in all patients, asymptomatic cases of RPED were undetected and therefore the incidence rate is likely an underestimate of this risk. Likewise, the incidence of hyperphosphatemia is confounded by the use of prophylactic phosphate binders in 48% of patients (that is, in the absence of hyperphosphatemia).

Among the 351 patients who received infigratinib across clinical trials, RPED occurred in 11% of patients. The median time to first onset of RPED was 26 days. RPED led to dose interruption/reduction of infigratinib in 3.4% of patients and permanent discontinuation in 0.6% of patients. In order to mitigate the risk of severe RPED, comprehensive ophthalmologic monitoring including optical coherence tomography is recommended prior to initiation of infigratinib, at 1 month, at 3 months and every 3 months thereafter during treatment.

The following has been extracted from Section 4.4 Special warnings and precautions for use of the Australian PI:

'Infigratinib can cause CSR/RPED, which may cause symptoms such as blurred vision. All clinical trials of infigratinib conducted frequent routine ophthalmic monitoring to detect asymptomatic CSR/RPED.

Perform a comprehensive ophthalmic examination including optical coherence tomography (OCT) prior to initiation of infigratinib, at 1 month, at 3 months, and then every 3 months thereafter during treatment. Refer patients for ophthalmic evaluation urgently for onset of visual symptoms, and follow-up every 3 weeks until resolution or discontinuation of infigratinib.

If a patient loses visual acuity with corresponding changes on macular OCT (PED-like or central serous retinopathy-like chorioretinopathy) continue current dose and review in 14 days. If resolving chorioretinopathy continue infigratinib, if getting worse or not resolving, reduce dose or cease treatment in conjunction with treating physician.'

Ocular effects: Dry eye

Among 351 patients who received infigratinib across clinical trials, dry eye occurred in 24% of patients, including Grade 3 in 0.3% of patients. No Grade 4 dry eye was observed.

Hyperphosphataemia

The following has been extracted from Section 4.4 Special warnings and precautions for use of the Australian PI:

‘Treat patients with ocular demulcents as needed.

Hyperphosphataemia and soft tissue mineralisation

Hyperphosphatemia is another series risk of infigratinib.

Among 108 patients who received infigratinib in Study CBGJ398X2204, hyperphosphatemia was reported in 89% of patients based on laboratory values above the upper limit of normal. Among 351 patients who received infigratinib across clinical trials, hyperphosphatemia was reported in 82% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 8 days (range: 1 to 349). Phosphate binders were received by 83% of patients who received infigratinib. The median time to onset of hyperphosphatemia was 8 days (range: 1 to 169).’

The following has been extracted from Section 4.4 Special warnings and precautions for use of the Australian PI:

‘Infigratinib can cause hyperphosphatemia leading to soft tissue mineralisation, cutaneous calcinosis, non-uremic calciphylaxis, vascular calcification, and myocardial calcification.

Increases in phosphate levels may occur as a pharmacodynamic effect of infigratinib.

Monitor for hyperphosphataemia throughout treatment. Initiate phosphate lowering therapy when serum phosphate is > 5.5 mg/dL. For serum phosphate > 7.5 mg/dL, withhold infigratinib and initiate phosphate lowering therapy. Withhold, dose reduce, or permanently discontinue infigratinib based on duration and severity of hyperphosphatemia.’

Risk management plan

The sponsor has submitted core risk management plan (RMP) version 0.0 (date 12 November 2020; data lock point (DLP) 31 March 2020) and Australia specific annex (ASA) version 0.0 (date 13 November 2020) in support of this application. The RMP has been prepared for Australia and Canada and is a core RMP intended to form the basis of future European Union (EU) RMP. The core RMP is not provided in the USA application as no risk evaluation and mitigation strategy (REMS) was required. In response to TGA questions, the sponsor supplied updated ASA version 1.0 (date 23 June 2021) in association with existing core RMP version 0.0. On request, sponsor has supplied updated core RMP version 1.0 (date 20 September 2021; DLP 1 March 2021) and ASA version 1.2 (date 21 September 2021) to support the decision on product registration.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6. Further information regarding the TGA’s risk management approach can be found in [risk management plans for medicines and biologicals](#) and [the TGA's risk management approach](#).

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED)	✓	✓ ²	✓	-
	Imbalance of calcium/phosphorus homeostasis	✓	✓ ²	✓	-
Important potential risks	Embryo-fetal toxicity	✓ ¹	-	✓	-
Missing information	Use in patients with severe hepatic impairment	✓	-	✓	-
	Use in patients with severe renal impairment	✓	-	✓	-

1 Targeted pregnancy follow-up questionnaire

2 FDA post-marketing study 4067-4 (per FDA's Infigratinib Approval Letter dated 27 May 2021)

There are no differences in the summary of safety concerns in the Core RMP and that proposed for Australia. There are no Australia specific safety concerns. The summary is considered acceptable.

Routine pharmacovigilance is proposed for all concerns, with the use of a targeted follow-up questionnaire to collect and evaluate specific data related to embryo-fetal toxicity in the post-marketing period. Activities described in Core RMP are the same as those proposed for Australia in the ASA. The sponsor has included US post-marketing study, Study 4067-4 in the ASA as an additional pharmacovigilance activity to further characterise safety concerns specified in Table 6 above.

The clinical study plan to support provisional registration of infigratinib is included in the ASA and includes a Phase II study, Study CBGJ398X2204 and a confirmatory Phase III study, Study QBGJ398-301. The format and content of the plan is in line with TGA guidelines. The Delegate agrees that the study plan is acceptable.

Routine risk minimisation activities are proposed to address all safety concerns in Australia. No additional risk minimisation activities are planned for Australia or other regions as detailed in the core RMP. This is considered acceptable. The sponsor agrees to undertaker closer monitoring of the potential for medication error in early years of marketing to confirm Truseltiq's packaging presentation and labelling is appropriate for the Australian patient population. The ASA commitment includes analyse 'risk of dosing error' as a safety topic in PSUR submissions to TGA. These measures are to promote safe and effective use of the product.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available

version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

‘The Infigratinib Core-Risk Management Plan (RMP) (version 1.0, dated 20 September 2021, data lock point 1 March 2021), with Australian specific annex (version 1.2, dated 21 September 2021), included with submission PM-2020-06031-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.’

The following wording is recommended for the PSUR requirement:

‘An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency’s Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.’

As Truseltiq is being considered for a provisional registration it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Truseltiq (infigratinib) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Truseltiq must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

As Truseltiq is being considered for a provisional registration the following wording regarding confirmatory trial data is recommended for the condition of registration:

Confirmatory trial data (as identified in the sponsor’s plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

Specifically the sponsor must conduct studies as described in the clinical study plan in version 1.0 (date 23 June 2021) of the Australia-Specific Annex. The following study report(s) should be submitted to TGA:

- Study CBGJ398X2204, ClinicalTrials.gov identifier NCT02150967, by second quarter of 2023
- Study QBGJ398-301, PROOF trial, by second quarter of 2027

Further guidance for sponsors is available on the TGA website.’

Risk-benefit analysis

Delegate's considerations

Cholangiocarcinoma is a rare cancer arising from epithelial cells of bile ducts and is the second most common primary liver tumour worldwide after hepatocellular carcinoma.

Fibroblast growth factor receptor 2 fusions have been detected in approximately 13% to 17% of intrahepatic CCA and these fusions generally lead to ligand-independent constitutive activation of the receptor and downstream MAPK-ERK and JAK-STAT signalling pathways. Infigratinib is a small molecule kinase inhibitor that is an ATP-competitive inhibitor of the fibroblast growth receptors.

There is no curative treatment for patients with advanced CCA. The standard of care for unresectable or metastatic disease is chemotherapy with cisplatin in combination with gemcitabine and median survival is less than a year.

The safety and effectiveness of infigratinib for the treatment of patients with advanced, unresectable CCA with FGFR2 fusions or other rearrangements and disease progression during or after systemic therapy was established by the results of Cohort 1 of an open label, single arm, international trial, Study CBGJ398X2204. Patients received infigratinib in 28-day cycles at a dosage of 125 mg orally once daily for 21 consecutive days, followed by 7 days off therapy. Infigratinib was administered until disease progression or unacceptable toxicity. The major efficacy outcome measures were overall response rate and duration of response as determined by a BIRC according to RECIST version 1.1.

The median age was 53 years (range: 23 to 81 years), 62% were female, 72% were White, and all but one patient had a baseline ECOG performance status score of less than 2 (ECOG PS 0: 42%; ECOG PS 1: 57%). Eighty one percent of patients had FGFR2 gene fusions and 17% had FGFR rearrangements. Among the patients with in-frame FGFR2 gene fusions, the most common FGFR2 fusion identified was FGFR2-BICC1 (27%). Ninety-four percent of patients had metastatic disease. All patients had received at least 1 prior line of systemic therapy, 32% and 29% had 2 or 3 prior lines of therapy, respectively.

The Study CBGJ398X2204 demonstrated a clinically meaningful and durable overall response rate in patients with previously treated, locally advanced or metastatic cholangiocarcinoma with a FGFR2 gene fusion or other rearrangement, a serious and life threatening disease. In the 108 patients with FGFR2 gene fusion/rearrangement-positive cholangiocarcinoma who received at least one dose of infigratinib, the estimated overall response rate was 23.1% (95% CI: 16%, 32%). At the time of the analysis, the median duration of response was 5.03 months (95% CI: 3.71, 9.26); 8 of the 25 responders (32%) maintained the response for at least six months.

The Study CBGJ398X2204 also provided the primary data to support the safety of infigratinib for the proposed indication. An additional 243 patients with a variety of cancers treated with infigratinib as a single agent in four other multicentre single arm trials or cohorts of the Study CBGJ398X2204 provided additional, supportive safety data. Although assessment of a causal relationship between infigratinib and treatment emergent reactions was limited given the single arm design of the trials providing safety data, the adverse reactions observed in patients treated with infigratinib were largely expected given the mechanism of action and the toxicity profile observed in preclinical studies. Among the 108 patients with cholangiocarcinoma enrolled in Study CBGJ398X2204, the most common adverse reactions to infigratinib (occurring at an incidence rate \geq 20%) are nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmar-plantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, vision blurred and

vomiting. The most common laboratory abnormalities were increased creatinine, and calcium-phosphate analyte abnormalities.

The serious risks of infigratinib include ocular toxicity (particularly retinal pigment epithelial detachment) and hyperphosphatemia. Given the lack of systematic optical coherence tomography assessments in all patients, asymptomatic cases of RPED were undetected and therefore the incidence rate is likely an underestimate of this risk. Likewise, the incidence of hyperphosphatemia is confounded by the use of prophylactic phosphate binders in 48% of patients (that is in the absence of hyperphosphatemia). Among the 351 patients who received infigratinib across clinical trials, RPED occurred in 11% of patients.

The median time to first onset of RPED was 26 days. RPED led to dose interruption/reduction of infigratinib in 3.4% of patients and permanent discontinuation in 0.6% of patients. In order to mitigate the risk of severe RPED, comprehensive ophthalmologic monitoring including ocular coherence tomography is recommended prior to initiation of infigratinib, at 1 month, at 3 months and every 3 months thereafter during treatment.

The Delegate noted following analysis of ocular safety, adapted from the US FDA's New Drug Application and Biologic License Application multi-disciplinary review and evaluation of infigratinib (Truseltiq).³⁰

Analysis of Submission-Specific Safety Issues: Ocular Disorder

Extract from US FDA's New Drug Application (NDA) and Biologic License Application (BLA) multi-disciplinary review and evaluation of infigratinib (Truseltiq)

Applicant's position:

Infigratinib, based on its mechanism of action, can cause Central Serous Retinopathy/Retinal Pigment Epithelial Detachment (CSR/RPED), which may cause symptoms such as blurred vision.

All clinical trials of infigratinib conducted frequent routine ophthalmic monitoring to detect asymptomatic CSR/RPED. Among 351 patients who received infigratinib across clinical trials (125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set), CSR/RPED occurred in 11% of patients, including Grade 3 CSR/RPED in 0.9%. No Grade 4 CSR/RPED was observed.

The median time to first onset of CSR/RPED was 26 days. CSR/RPED led to dose interruption/reduction of infigratinib in 3.4% of patients, and permanent discontinuation in 0.6 % of patients. Among 351 patients who received infigratinib across clinical trials, dry eye events occurred in 24% of patients, including Grade 3 in 0.3% of patients. No Grade 4 dry eye was observed.

FDA assessment:

Because ocular toxicities are a class effect of FGFR inhibitors, an ophthalmology consult was obtained to assist with the assessment of ocular toxicities. Approximately 15% of patients experienced RPED, 21% had vision blurred, and 44% of patients experienced dry eye (in FDA analysis, using grouped preferred terms dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis;

³⁰ https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214622Orig1s000MultidisciplineR.pdf

these terms were grouped as there are alternative terms for an equivalent event). As stated in FDA's ophthalmology review, CTCAE grades are not considered reflective of the severity of ocular events and are not recommended to be used for these ocular events. Specifically, whether or not the RPED was resolving was more indicative, compared to CTCAE grade, of severity of injury and long-term sequelae and, thus, this approach was used in Section 2 of the USPI.

In the pooled safety population (351 patients receiving infigratinib at the indicated dose), CSR/RPED occurred in 11% of patients. The median time to first onset of CSR/RPED was 26 days and led to dose interruption/reduction of infigratinib in 3.4% of patients, and permanent discontinuation in 0.6% of patients. Of note, the incidence of asymptomatic RPED is likely to be higher than the 15% reported on Study CBGJ398X2204 because not all patients had systematic monitoring with optical coherence tomography (OCT) (only 78% of patients had a post-baseline exam).

Because ocular toxicity is an important risk for patients, Section 5.1 of the Truseltiq USPI states: 'Perform a comprehensive ophthalmic examination including OCT prior to initiation of Truseltiq, at 1 month, at 3 months, and then every 3 months thereafter during treatment. Refer patients for ophthalmic evaluation urgently for onset of visual symptoms, and follow-up every 3 weeks until resolution or discontinuation of Truseltiq'. This routine screening must be carried out in concert with ophthalmologists because the necessary procedures, such as OCT, are not generally performed outside of ophthalmology offices.

Extracted from: NDA214622 Multi-disciplinary Review and Evaluation for Infigratinib (Truseltiq). US Food and Drug Administration. January 2020, p188-189.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214622Orig1s000MultidisciplineR.pdf

The Delegate also noted the following, from the publication by Javle et al. 2021:²⁸

'Central serous retinopathy-like and retinal pigment epithelial detachment-like events occurred in 18 (17%) patients, of which ten (9%) were grade 1, seven (6%) were grade 2, one (1%) was grade 3, none were grade 4, and none were serious. The most common central serous retinopathy-like and retinal pigment epithelial detachment-like events were the appearance of chorioretinopathy (n = 10), subretinal fluid (n = 6), and serous retinal detachment (n = 3). The median time to first onset of central serous retinopathy-like or retinal pigment epithelial detachment-like events was 39 days (IQR [interquartile range] 15–93) and two patients discontinued treatment because of central serous retinopathy or retinal pigment epithelial detachment. Central serous retinopathy-like and retinal pigment epithelial detachment-like events are part of the adverse event of special interest of eye disorder. The median time to first onset of an eye disorder was 25 days (IQR [interquartile range] 15–65).'

Among 108 patients who received infigratinib in Study CBGJ398X2204, hyperphosphatemia was reported in 89% of patients based on laboratory values above the upper limit of normal. Among 351 patients who received infigratinib across clinical trials, hyperphosphatemia was reported in 82% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 8 days (range 1 to 349). Phosphate binders were received by 83% of patients who received infigratinib. The median time to onset of hyperphosphatemia was 8 days (range 1 to 169).

Overall, the toxicity profile of infigratinib is considered acceptable when considering the anti-tumour effects (that is durable responses) in patients with previously treated cholangiocarcinoma harbouring a FGFR2 fusion or other rearrangement, who have a poor life expectancy and limited treatment options. The risks of infigratinib are toxicities that oncologists are well trained to manage, are largely reversible with dosage modification

and supportive care, and overall are acceptable for a population with a serious and life threatening condition.

Proposed action

Overall, the benefit/risk assessment is considered positive and sufficient to support provisional approval of infigratinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. *Could the sponsor provide an update on the availability of next gen sequencing in Australia to identify patients with FGFR2 fusions or rearrangements?*

Foundation Medicine's FoundationOne CDx (F1CDx; tissue-based) and FoundationOne Liquid CDx (F1LCDx; plasma-based) tests are both currently available in Australia to identify patients with FGFR2 fusions or rearrangements. Both tests are next-generation sequencing.

Independent expert advice

The Delegate received the following independent expert advice.

1. *Can independent expert provide a clinical opinion, based on the summary data available, on the seriousness of the ocular toxicity associated with infigratinib, in the context of patients being treated for metastatic cholangiocarcinoma?*

The expert is of view that the ocular side effects of infigratinib outlined in Jarvis M et al Lancet are not very detailed and unfortunately the outcome of the two patients that developed PED/central serous retinopathy and ceased treatment, have not been outlined. However, in the context of patients being treated for metastatic cholangiocarcinoma, safe ocular screening protocols can be derived from the study.

2. *Does independent expert agree with the FDA's ophthalmology review that 'CTCAE grades are not considered reflective of the severity of ocular events and are not recommended to be used for these ocular events?'*

The expert is of view that the CTCAE grades are not specific about the severity of ocular events. They also do not provide recommendations of what to do if/when they occur.

The expert has concerns about the retinopathy/pigment epithelial detachment (PED) ocular side effects is that management of PED and central serous retinopathy are grouped together, despite each having differing prognosis in the clinical settings. A PED that is not central and not affecting visual acuity could be safety monitored even if it didn't resolve by 14 days.

The expert is of view that the recommendations of the FDA's ophthalmology review for dry eye is appropriate.

3. *Do you agree with the recommendations on routine ophthalmic screening?*

The expert is of view that baseline ophthalmic screening with one month, then three monthly reviews with OCT is appropriate for recommendation of patients taking infigratinib. This would mean that the ophthalmologist could both advise patients on dry eye treatment measures prior to developing the problem (which occurred in 44%) and also monitor for asymptomatic CENTRAL SEROUS RETINOPATHY-like retinopathy and PED retinopathy.

The expert is of view that the recommendation on what to do in the event in of a patient developing a PED is not appropriate. PEDs that are not central do not cause vision loss and are often asymptomatic. On the other hand, serous retinal detachments and subretinal fluid (which are the same thing) when central can cause vision loss. The expert recommends making a recommendation on central serous retinopathy rather than PED.

The expert is of view that there is overlap of diagnosis (serous retinal detachment = subretinal fluid) and it is not clear if the central serous retinopathy or PED has caused vision loss in the patients who have been reported to have ocular side effects. The expert is of view that making the recommendation on what to do in layman's term could be an option.

The expert recommends a statement like... 'If a patient loses visual acuity with corresponding changes on macular OCT (PED-like or central serous retinopathy-like chorioretinopathy) continue current dose and review in 14 days. If resolving chorioretinopathy continue infigratinib, if getting worse or not resolving, reduce dose or cease treatment in conjunction with treating physician.' in the product information.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines ACM for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the provisional registration of Truseltiq (infigratinib) 25 mg, 100 mg, hard capsule, blister pack, indicated for:

Truseltiq has provisional approval in Australia 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 decision to approve this indication has been made on the basis of overall response rate and duration of response in a single arm trial. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

Specific conditions of registration applying to these goods

- Truseltiq (infigratinib) is to be included in the Black Triangle Scheme. The PI and CMI for Truseltiq must include the black triangle symbol and mandatory accompanying text for the product's entire period of provisional registration.
- The infigratinib core-RMP (version 1.0, dated 20 September 2021, DLP 1 March 2021) with ASA (version 1.2, dated 21 September 2021), included with Submission PM-2020-06031-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of RMP is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be

submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

Specifically, the sponsor must conduct studies as described in the clinical study plan in version 1.0 (dated 23 June 2021) of the Australia specific annex. The following study report(s) should be submitted to the TGA:

- Study CBGJ398X2204, ClinicalTrials.gov identifier NCT02150967, by the second quarter in 2023
- Study QBGJ398-301, the PROOF trial, by the second quarter in 2027.

Further guidance for sponsors is available on the TGA website.

Attachment 1. Product Information

The PI for Truseltiq approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA [PI/CMI search facility](#).

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