Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Fruzaqla

Active ingredient: Fruquintinib

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

August 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
%CV	Percent coefficient of variation
ACM	Advisory Committee on Medicines
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific annex
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
AUC_{0-24}	Area under the concentration time curve from time 0 to 24 hours
BCRP	Breast cancer resistance protein
BSC	Best supportive care
CI	Confidence interval
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CRC	Colorectal cancer
CYP	Cytochrome P450 enzymes
DLP	Data lock point
dMMR	Deficient mismatch repair
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ER	Exposure ratio
ERAUC	Exposure ratio based on area under the concentration-time curve
EU	European Union
FDA	United States Food and Drug Administration
HER2	Human epidermal growth factor receptor 2
IC_{50}	Concentration that achieves 50% inhibition
MATE	Multidrug and toxin extrusion protein
mCRC	Metastatic colorectal cancer
MSI-h	Microsatellite instability-high
NCCN	National Comprehensive Cancer Network

Abbreviation	Meaning
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptides
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PRES	Posterior reversible encephalopathy syndrome
PSUR	Periodic safety update report
RMP	Risk management plan
TAS-102	Trifluridine/tipiracil
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
USA	United States of America
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptors

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Fruzaqla
Active ingredient:	Fruquintinib
Decision:	Approved
Date of decision:	1 October 2024
Date of entry onto ARTG:	2 October 2024
ARTG numbers:	422038 and 422039
, *Black Triangle Scheme*	Yes
for the current submission:	
Sponsor's name and address:	Takeda Pharmaceuticals Australia Pty Ltd Grosvenor Place Level 39, 225 George Street, Sydney, NSW, 2000 Australia
Dose form:	Capsule
Strengths:	1 mg and 5 mg
Container:	Bottle
Pack size:	21 capsules
Approved therapeutic use for the current submission:	*Fruzaqla is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, and an anti-EGFR agent if appropriate.*
Route of administration:	Oral
Dosage:	Fruzaqla should be initiated by a physician experienced in the administration of anticancer therapy. The recommended dose of Fruzaqla is 5 mg taken orally once daily (at approximately the same time each day) for the first 21 days of each 28-day cycle. Fruzaqla capsules should be swallowed whole and can be taken with or without food. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
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.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database 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.

Product background

This AusPAR describes the submission by Takeda Pharmaceuticals Australia Pty Ltd (the sponsor) to register Fruzaqla (fruquintinib) 1 mg and 5 mg, hard capsule, bottles for the following proposed indication:[1]

> *Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.*

The disease

Based on the most recent observed (2019/2021) and predicted (2023) data from the Australian Institute of Health and Welfare, colorectal cancer (CRC) is the fourth most commonly diagnosed cancer (9% of cancers) and second most commonly fatal cancer (10% of cancer deaths) in Australia.[2] Five-year survival rates have increased from 55% in the late 20th century (1990 to 1994) to 71% in recent years (2015 to 2019).[2] Colorectal cancer is more common in males than females,[2] and incidence appears to have been increasing in cohorts born in the late 1970s onward: the incidence of colon cancer in people born between 1988 and 1992 is triple that of those born between 1943 and 1947.[3] These trends are strongly suggestive of changing exposures in successive generations, and a similar trend has been described in the United States of America (USA).[4]

Current treatment options

Unlike other solid tumours, resection of single organ (lung or liver) metastases may be curative in around half of patients with metastatic CRC (mCRC) treated in this manner.[5] Resection of multi-organ oligometastatic disease may also be considered by careful multidisciplinary selection, and neoadjuvant systemic therapy may be integrated to downstage disease.[5] In recent

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Bowel cancer (Colorectal cancer) in Australia statistics (web page). Cites data source as the Australian Institute of Health and Welfare (AIHW). Updated 3 January 2024. Accessed 3 June 2024 at: https://www.canceraustralia.gov.au/cancer-types/bowel-cancer/statistics

[3] Feletto E, et al. Trends in Colon and Rectal Cancer Incidence in Australia from 1982 to 2014: Analysis of Data on Over 375,000 Cases. Cancer Epidemiol Biomarkers Prev. 2019 Jan;28(1):83-90.

[4] Siegel RL, et al. Colorectal cancer incidence patterns in the United States, 1974–2013. J Natl Cancer Inst 2017;109.

[5] Brown KG., et al. Contemporary management of advanced colorectal cancer: the Australian experience. Med J Aust. 2024 Mar 18;220(5):222-224.

decades, median overall survival for patients with mCRC in clinical trials has increased from 23 months for patients diagnosed between 2004 and 2012 to 32 months for patients diagnosed between 2013 and 2015.[6] Nevertheless, mCRC remains a life-threatening and seriously debilitating disease, with a 5-year survival rate of 16%.[7] For most patients with mCRC, a cure is not able to be achieved and palliative systemic therapy is considered.[5]

In Australia, standard systemic treatment approaches for mCRC are in keeping with major international guidelines such as those published by the National Comprehensive Cancer Network (NCCN) in the USA.[5, 8] Treatment is continued until disease progression or unacceptable toxicity.[9]

For patients with tumours that test positive for deficient mismatch repair (dMMR)/ microsatellite instability-high (MSI-h), first-line systemic treatment is immunotherapy with a checkpoint inhibitor.[8] Pembrolizumab is approved in Australia for this indication.[10] Based on retrospective analyses of molecular data, tumours harbouring a pathogenic polymerase epsilon mutation are expected to respond similarly,[11] and such tumours are included alongside dMMR/MSI-h tumours in the NCCN guideline.[8]

For microsatellite stable/mismatch repair proficient tumours, first-line systemic treatment usually consists of a fluoropyrimidine-based chemotherapy regimen (often fluorouracil and leucovorin, sometimes capecitabine) plus either oxaliplatin (for example Folfox) or irinotecan (for example Folfiri) or both (for example Folfirinox) with an anti-vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab).[8] For left-sided and KRAS/NRAS/BRAF wild-type tumours, an anti-epidermal growth factor receptor (EGFR) antibody can be used in place of the anti-VEGF agent.[8] Modifications such as intensified, triple-agent chemotherapy with both oxaliplatin and irinotecan (Folfirinox), treatment holidays or deintensification may be used.[8]

Second-line and subsequent treatment options include the same regimens (excluding oxaliplatin and/or irinotecan re-treatment), plus a number of targeted therapies that may be used where the tumour demonstrates carriage of the appropriate biomarker.[8] These are: encorafenib plus cetuximab (for BRAF V600E mutation-positive CRC),[12] and entrectinib or larotrectinib for neurotrophic tyrosine receptor kinase gene fusion-positive tumours.[13, 14] Tucatinib in combination with trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive

[6] Zeineddine FA., et al. Survival improvement for patients with metastatic colorectal cancer over twenty years. NPJ Precis Oncol. 2023 Feb 13;7(1):16.

[7] Surveillance, Epidemiology and End Results Program (SEER) [USA]. Cancer Stat Facts: https://seer.cancer.gov/statfacts/html/colorect.html

[8] National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2024 Colon Cancer. Accessed 17 JUN 2024 at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

[9] EviQ Australian regimen guidelines – multiple regimens – for metastatic colorectal carcinoma (CRC). Accessed 18 JUN 2024 at: https://www.eviq.org.au/medical-oncology/colorectal/metastatic

[10] Australian Product Information (PI) for pembrolizumab (KEYTRUDA). Last updated 1 MAY 2024. Accessed 17 JUN 2024 at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2023-PI-01512-1

[11] Garmezy B, et al. Clinical and Molecular Characterization of POLE Mutations as Predictive Biomarkers of Response to Immune Checkpoint Inhibitors in Advanced Cancers. JCO Precis Oncol. 2022 Feb;6:e2100267.

[12] Australian Product Information (PI) for encorafenib (BRAFTOVI). Last updated 15 DEC 2023. Accessed 19 JUN 2024 at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2019-PI-01022-1

[13] Australian Product Information (PI) for entrectinib (ROZLYTREK). Last updated 22 DEC 2023. Accessed 19 JUN 2024 at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-01721-1&d=20240619172310101

[14] Australian Product Information (PI) for larotrectinib (VITRAKVI). Last updated 12 OCT 2023. Accessed 19 JUN 2024 at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-02289-1&d=20240619172310101

CRC received provisional TGA approval in November 2023,[15] but a product information document is not available for tucatinib on the Australian Register of Therapeutic Goods (ARTG) search page,[16] suggesting tucatinib might not be being supplied in Australia. Additional targeted options are in NCCN guidelines but do not have regulatory approval for such indications in Australia: trastuzumab deruxtecan for HER2-amplified (IHC 3+) CRC, sotorasib or adagrasib plus an EGFR inhibitor for KRAS G12C mutated CRC, and selpercatinib for RET gene fusion-positive CRC.[8]

For disease that has progressed through all available regimens, the NCCN guideline includes as options regorafenib, trifluridine/tipiracil (also known as TAS-102) with or without bevacizumab (with bevacizumab is preferred) and fruquintinib. Regorafenib and TAS-102 are both registered for this indication in Australia.[17, 18] The indication for regorafenib does not specifically exclude use in combination with bevacizumab but does not specify it either, and the approved indications for bevacizumab in Australia only include treatment of mCRC in combination with fluoropyrimidine-based chemotherapy (that is, first or second line).[19]

Best supportive care (BSC) is an option at any line.[8] Recent real-world data suggest that around 30% of patients in the USA receive BSC in the second line, and of the remainder, 15% receive regorafenib and 12% receive trifluridine/tipiracil.[20]

Clinical rationale

Fruquintinib is a small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3 (with IC50 values of 33, 35, and 0.5 nM, respectively), with antitumor effects resulting from suppression of tumour angiogenesis.

Vascular endothelial growth factor mediated endothelial cell proliferation, and tubular formation were inhibited by fruquintinib *in vitro*. *In vitro* and *in vivo* studies showed fruquintinib inhibited VEGF-induced VEGFR-2 phosphorylation. Fruquintinib was shown to inhibit tumour growth in tumour xenograft mouse models.

Regulatory status

Australian regulatory status

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

[15] https://www.tga.gov.au/resources/prescription-medicines-registrations/tukysa-merck-sharp-dohme-australia-pty-ltd

[16] Australian Register of Therapeutic Goods (ARTG). Entry for tucatinib. Searched 19 JUN 2024 at: https://www.ebs.tga.gov.au/

[17] Australian Product Information (PI) for regorafenib (STIVARGA). Last updated 10 FEB 2021. Accessed 27 JUN 2024 at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02451-1&d=20240627172310101

[18] Australian Product Information (PI) for trifluridine / tipiracil hydrochloride (STIVARGA). Last updated 20 JUN 2022. Accessed 27 JUN 2024 at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-01847-1

[19] Australian Product Information (PI) for bevacizumab (ABEVMY). Last updated 15 MAY 2023. Accessed 5 JUL 2024 at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2021-PI-02226-1

[20] Desai K, et al. Real-world treatment patterns and unmet need in patients with previously treated metastatic colorectal cancer that is not MSI-H or dMMR [meeting abstract]. JCO 42, 53-53(2024).

International regulatory status

This submission was evaluated as part of the Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium with work-sharing between the TGA, Health Canada, Health Sciences Authority Singapore, Swissmedic and the Medicines and Healthcare Products Regulatory Agency. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

This evaluation was also facilitated through Project Orbis, an initiative of the United States Food and Drug Administration (FDA) Oncology Center of Excellence. Under this project, the FDA, Health Canada, Health Sciences Authority (Singapore), Swissmedic (Switzerland), Medicines and Healthcare products Regulatory Agency (United Kingdom) and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
China	12 May 2017	Approved on 4 September 2018	*This product is indicated for patients with metastatic colorectal cancer (mCRC) who have received fluorouracil, oxaliplatin and irinotecan-based chemotherapy, and received or are unsuitable to receive anti-vascular endothelial growth factor (VEGF) therapy, and if RAS wild type, an anti-epidermal growth factor receptor (EGFR) therapy.*
United States of America	30 March 2023	Approved on 8 November 2023	*Fruzaqla is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, an anti VEGF therapy, and, if RAS wild type and medically appropriate, an anti-EGFR therapy.*

Region	Submission date	Status	Approved indications
European Union	25 May 2023	Approved on 20 June 2024	*Fruzaqla as monotherapy is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin, and irinotecan based chemotherapies, anti VEGF agents, and anti EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine tipiracil or regorafenib.*
Canada	14 September 2023	Under consideration	Under consideration
Singapore	28 September 2023	Under consideration	Under consideration
Switzerland	28 September 2023	Under consideration	Under consideration

Fruquintinib was first approved in China, with the brand name Elunate, in September 2018. In early 2023 HUTCHMED (China) Ltd entered into a licensing agreement with Takeda for further commercialisation of fruquintinib outside of China, Hong Kong and Macau.

Registration timeline

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

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2023-04088-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	30 October 2023
First round evaluation completed	26 February 2024
Sponsor provides responses on questions raised in first round evaluation	23 April 2024
Second round evaluation completed	11 June 2024
Delegate's[21] Overall benefit-risk assessment and request for Advisory Committee advice – Interim	8 July 2024

[21] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health, Disability and Ageing who decided the submission under section 25 of the Act.

Description	Date
Sponsor's pre-Advisory Committee response	19 July 2024
Advisory Committee meeting	1 and 2 August 2024
Delegate's Overall benefit-risk assessment – Final	19 August 2024
Registration decision (Outcome)	1 October 2024
Administrative activities and registration in the ARTG completed	2 October 2024
Number of working days from submission dossier acceptance to registration decision*	165

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

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.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

EMA: ICH Topic Q3A (R2) Note for Guidance on Impurities Testing: Impurities in New Drug Substances (CPMP/ICH/2737/99)TGA-adopted, effective date: October 2006

- EMA: ICH Topic Q3B (R2) Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99)

  TGA-adopted, effective date June 2006

- EMA: ICH Topic S9 Guideline on Non-clinical Evaluation for Anticancer Pharmaceuticals (EMA/CHMP/ICH/646107/2008)

  TGA-adopted, effective date: May 2010

- EMA: ICH Topic S10 Guideline on Photosafety Evaluation of Pharmaceuticals (EMA/CHMP/ICH/752211/2012)

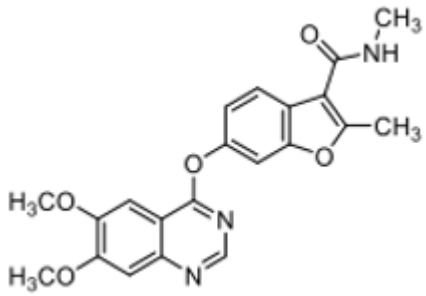
  TGA-adopted, effective date: June 2014

Quality

Drug substance

Fruquintinib is a small molecule antitumor quinazoline class, highly selective, potent, oral tyrosine kinase inhibitor.

Figure 1: Structure of fruquintinib



Fruquintinib is chemically synthesised and is jet-milled. It exhibits polymorphism as crystalline Form I. Fruquintinib has low solubility across the physiological pH range. Based on a maximum 5 mg dose, it meets the definition of a biopharmaceutical classification system low soluble drug substance.

The drug substance specification provided by the sponsor adequately controls the quality of the drug substance. Of note, single specified impurities are adequately controlled in accordance with the impurities in new drug substances scientific guideline (ICH Q3A (R2)). Particle size limits are based on the drug substance batches used in the clinical studies and polymorphic form is controlled by X-ray powder diffraction.

Drug product

The drug product is formulated as a dry blend encapsulated in a hard gelatin capsule. The 1 mg and 5 mg strengths are direct scales. They are differentiated by colour and imprinting. The 1 mg capsule is white to off-white powder filled into a hard gelatin capsule with standard yellow opaque cap and white opaque body, imprinted with 'HM013' over '1mg' on the body in black ink. The 5 mg capsule is white to off-white powder filled into a hard gelatin capsule with red opaque cap and white opaque body, imprinted with 'HM013' over '5mg' on the body in black ink.

The manufacturing process was adequately validated. The specification adequately controls the quality of the capsules. The single impurities are controlled in accordance with the impurities in new drug products scientific guideline (ICH Q3B(R2)). The dissolution method was demonstrated to be discriminatory. The dissolution limits were based on the clinical trial batches.

The nitrosamine risk assessment was acceptable and did not raise any nitroso-impurities of concern. The proposed child-resistant closure met TGA requirements. The stability data supported the proposed shelf-life of 24 months when stored below 30 °C.

Biopharmaceutics

There have been no changes to the product or to the manufacturing process during or after the clinical program. As such, no bioequivalence bridging studies have been evaluated.

An additional new site of manufacture is proposed for manufacture of the commercial product. Satisfactory *in vitro* data was provided to bridge the product used in the Phase III study and the proposed site.

Quality conclusion

The Product Information (PI) and labelling are considered acceptable from a pharmaceutical quality perspective.

The quality evaluation concluded with a recommendation of approval from a pharmaceutical chemistry perspective.

Nonclinical

Fruquintinib is a small molecule kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3, which inhibits VEGF-mediated endothelial cell proliferation and tubular formation *in vitro* and inhibits VEGF-induced VEGFR-2 phosphorylation *in vitro* and *in vivo*. Fruquintinib inhibited tumour growth in a xenograft murine model of colon cancer.

There is one major circulating metabolite of fruquintinib, M11, which is active but more than 10 times less potent than the parent drug (IC_{50} of 0.033 µM versus fruquintinib IC_{50} of 0.002 µM)[22].

There is low likelihood of QT interval prolongation in humans,[23] based on *in vitro* human ether-a-go-go related gene assays in which fruquintinib (IC_{50} > 13.08 µM, $ER_{Cmax\ (unbound)}$ ~360)[24] and metabolite M11 (IC_{50} > 6.05 µM, $ER_{Cmax\ (unbound)}$) > 1300) did not inhibit human ether a go go related gene channels.

Potential for interactions as a victim:

- Fruquintinib metabolism is mainly CYP3A4 mediated, with minor contributions from CYP2C8, CYP2C9 and CYP2C19.[25] Therefore, drugs that affect CYP3A4 may significantly alter exposure to fruquintinib.
- Fruquintinib was not a substrate of P-glycoprotein (P-gp), OATP1B1 or OATP1B3 *in vitro*. No data on fruquintinib as a substrate of other transporters was provided, which was considered acceptable given its high permeability in the Caco-2 cell assay and its metabolic elimination.

Potential for interactions as a perpetrator:

- Fruquintinib (10 µM) did not induce CYP1A2, CYP2B6, or CYP3A4 *in vitro*.
- Fruquintinib did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 *in vitro*. There was no notable inhibition of OATP1B1, OATP1B3,[26] OAT1, OAT3, OCT2,[27] MATE1, and MATE2-K[28] at clinically relevant concentrations.
- Fruquintinib inhibited P-gp (IC_{50} 4.60 µM) and breast cancer resistance protein (BCRP) (IC_{50} 1.29 µM) in a dose dependent manner. Clinical studies were performed, and did not substantiate this as a clinically relevant concern.

Metabolite potential for interactions:

- Metabolite M11 did not show significant reversible inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 (IC_{50} > 50 µM). Metabolite M11 demonstrated a weak reversible inhibitory effect on CYP3A4/5 (IC_{50} 38 µM). Metabolites M9 and M11 did not have time dependent inhibitory effects on CYP1A2, CYP2C9, CYP2D6, and CYP3A4/5.

[22] IC50 = concentration that achieves 50% inhibition.

[23] 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.

[24] ER = animal-to-human exposure ratio (subscript indicates parameter used to calculate ratio).

[25] CYP = Cytochrome P450 enzymes.

[26] OATP = organic anion transporting polypeptides.

[27] OAT = organic anion transporter.

[28] MATE = multidrug and toxin extrusion protein.

Metabolite M11(10 μM) demonstrated low potential to inhibit OATP1B1, OATP1B3, MATE1, MATE2-K, OAT1, OAT3, and OCT2 (IC_{50} > 10 μM).

- Metabolite M11 inhibited BCRP (IC_{50} 1.03 μM, compared with clinical free maximum concentration (C_{max}) 4.6 nM) and showed a weak potential to inhibit P-gp (maximum inhibition of 42.6% at 20 μM) *in vitro*. Metabolite M9 inhibited BCRP (IC_{50} 7.60 μM) and did not inhibit P-gp significantly. *In vitro* transporter inhibition data indicated no interactions perpetrated by metabolite M11 through inhibition of intestinal BCRP.

Notable target organs/systems for toxicity in non-clinical studies were:

- Gastrointestinal toxicity (diarrhea and gastrointestinal bleeding, degeneration, necrosis, and inflammation in the Brunner's gland)
- Hepatobiliary toxicity (elevated alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol, and triglycerides, along with hepatocyte necrosis/degeneration, hepatocyte swelling, vacuolation, granulomatous inflammation and bile duct hyperplasia)
- Pancreatic toxicity:
  - Increased amylase and lipase levels were observed in the 4-week rat study, indicating potential pancreatic toxicity at > 20 mg/kg/day (exposure ratio based on area under the concentration-time curve (ERAUC) > 7.8). There were no correlating histological findings, and the finding was only seen in females in one study. The nonclinical evaluation considered this an adverse finding, and that the above treatment-related finding observed in animal studies should be included in the risk management plan (RMP).
- Nephrotoxicity (elevated blood urea nitrogen, degeneration of renal glomerulus, and hyaline casts, vacuolation of tubular epithelial cells, urine protein)
- Adrenal gland (congestion, vacuolation and haemorrhage)
- Haematopoietic toxicity (decreased haematopoietic cells in the bone marrow)
- Immunotoxicity (decreased lymphocytes and atrophy of thymus, atrophy of spleen, mast cell infiltration in the mesenteric lymph nodes).

Fruquintinib was not mutagenic or clastogenic in standard genotoxicity testing; Ames test, *in vitro* chromosomal aberration assay (in Chinese hamster ovary cells) and *in vivo* bone marrow micronucleus test (in rats) with inclusion of an alkaline comet assay.

Except for bile duct hyperplasia, no pre-neoplastic lesions were noted in repeat-dose, nonclinical toxicity studies. Dedicated carcinogenicity studies were not submitted. In accordance with the nonclinical evaluation for anticancer pharmaceuticals scientific guideline (ICH S9), this is acceptable, in context of the proposed indication for use. If it was proposed that fruquintinib should be extended to usage in patients at earlier stages of disease, including patients with potentially resectable metastases, this would need to be re-visited.

Fruquintinib shows association with melanin-containing tissues, and significant absorption of photons with wavelengths within the region of 290 to 700 nm. Peak absorbance within this range was at 238 and 320 nm, associated with a molar extinction coefficient of 69367 and 11143 L·mol-1·cm-1, respectively. In accordance with the photosafety evaluation of pharmaceuticals scientific guideline (ICH S10) potential phototoxic effects of fruquintinib on skin was studied in guinea pigs following single oral dosing with fruquintinib (0, 5, 25 and 100 mg/kg) and exposure to light at ultraviolet A wavelength. No signs of dermal phototoxicity

were observed up to 100 mg/kg, ERAUC 16 (ER_{Cmax} 22). Ocular phototoxicity was not examined in the nonclinical studies.

In rats, fruquintinib treatment was associated with post-implantation loss and reduced fetal survival at 0.25 mg/kg/day (ERAUC 0.2). Fetal anomalies were also observed, including external (head and tail malformations and oedema), visceral (increase in malformations of malpositioned or absent blood vasculature) and skeletal (vertebral anomalies, unossified forelimb metacarpals and/or phalanxes) anomalies. The no observed adverse effect limit for maternal effects was 0.1 mg/kg/day (ERAUC 0.05) and for fetal development was 0.025 mg/kg/day (ERAUC 0.02). Since these effects were observed at exposures that were substantially lower than those achieved clinically, fruquintinib is highly likely to cause serious harm to the developing fetus at clinical exposures during pregnancy. Based on the nonclinical studies and pharmacological data, embryofetal toxicity is expected if fruquintinib is administered to pregnant patients at the proposed clinical dose. Pregnancy category D is recommended.

Evaluation of the nonclinical data package found it adequate for a drug for the treatment of patients with advanced cancer. All pivotal safety-related studies were Good Laboratory Practice (GLP) compliant.

The nonclinical evaluation concluded that there were no nonclinical objections to the registration of Fruzaqla for the proposed indication provided adverse effects in patients are manageable.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- 12 Phase I studies
- 6 Phase II studies
- 5 Phase III studies
- One Phase IV study

Pharmacology

The proposed dose is 5 mg of fruquintinib orally daily (agnostic of recency of feed intake) for the first 21 days of each 28-day cycle. This dosing schedule is referred as 3/1 (3 weeks on/1 week off) in this AusPAR.

This dose was selected based on pharmacokinetics (PK) and safety information obtained from a dose escalation trial and a randomised dose ranging trial. In the dose escalation trial, the maximum tolerated dose was determined to be 4 mg for daily continuous dosing, or 6 mg for daily dosing on a 3/1 schedule. The 4 mg daily continuous and 5 mg daily 3/1 dosing regimens were evaluated in a trial in patients with mCRC. The 5 mg daily 3/1 regimen showed better safety, was selected as the recommended Phase II dose, and was used in the randomised Phase III studies FRESCO and FRESCO-2.

The formulation proposed for marketing in Australia is the same as the formulation used in FRESCO-2.

Pharmacokinetics

Fruquintinib demonstrates linear PK over the dose range of 1 mg to 6 mg daily, which was well described by a one compartment model with first order absorption and linear elimination.

Absorption

Median time to maximum concentration (T_{max}) for a 5 mg single dose of fruquintinib under fasted conditions in healthy subjects was approximately 3 hours (range: 1.5 to 8). Absolute bioavailability has not been determined.

Food effect

Administration (5 mg) fasted is bioequivalent to administration with a high-fat, high-calorie meal. In the pivotal Phase III study (FRESCO-2), fruquintinib was administered irrespective of food intake. Co-administration of gastric pH-modifying agents (rabeprazole) did not affect fruquintinib PK.

Distribution

Daily oral administration of 5 mg fruquintinib reaches steady state exposure after 14 days, with an accumulation ratio of around 4 (based on area under the concentration time curve from time 0 to 24 hours (AUC_{0-24})). The geometric mean (percent coefficient of variation (%CV)), C_{max} and AUC_{0-24} were 300 ng/mL (28%) and 5880 ng·h/mL (29%), respectively, at the recommended dose in patients with advanced solid tumours.

Fruquintinib does not distribute into blood cells (the range of individual blood to plasma ratios from 0 to 120 hours post dose was 0.41 to 0.81). Plasma protein binding is approximately 95%. Apparent volume of distribution was 44 L in healthy subjects, and apparent volume of distribution was 48.5 L for a 70 kg patient with cancer at steady state estimated by population pharmacokinetic (PopPK) analysis.

Based on *in vitro* assays, fruquintinib is not a substrate for P-gp, OATP1B1, or OATP1B3.

Metabolism and elimination

Fruquintinib undergoes extensive metabolism including through mono- and di-oxidation, N- or O-demethylation, splitting off of the quinazoline moiety, amide bond hydrolysis, glucuronidation, and sulfation. Twenty-two unique metabolites were identified in the mass balance study, including the major plasma metabolite (17%) N-demethylation product 'M11'. Parent drug made up 72% of circulating radiolabelled material.

The M11 to parent ratio was 0.32 (based on AUC_{0-24}), but M11 is less than 10% as potent, so the potency-adjusted exposure of M11 is estimated at < 5% of total pharmacological activity of fruquintinib.

Elimination is predominantly metabolic. Only 6% of the dose was accounted for by excreted parent compound (5% faecal and < 1% urinary), and there was no significant excretion of M11. There are two main metabolic pathways. One via CYP3A4/5 and the other one via unidentified non-CYP enzymes (the 'M205 pathway'). Cytochrome P450 isoenzyme 3A4 (CYP3A4) is the main CYP contributing to M11 formation with minor contributions from CYP2C8, CYP2C9, and CYP2C19.

Fruquintinib apparent clearance was esimated at 13.2 mL/min for a 70 kg cancer patient in popPK analyses, consistent with Phase I observations. The mean (standard deviation) half-life of fruquintinib was 34 hours, in support of the studied daily dosing strategy.

Dose individualisation

Population PK analysis showed no clinically relevant effects of sex, body weight (range 36 to 158 kg; 5th and 95th percentiles 48 kg and 108 kg, respectively), age (18 to 82 years), Eastern Cooperative Oncology Group (ECOG), race (140 Asian patients, 29 Black patients, and 359 White patients), country (80 patients in China, 45 patients in Japan or 432 patients in the rest of the world) or health status (cancer patients or healthy subjects) on the PK of fruquintinib and M11. Body weight and health status were statistically significant covariates, but the magnitude of effect on exposure (< 20% and < 5%, respectively) was not clinically relevant.

No dose adjustment is needed in patients with mild hepatic impairment (total bilirubin ≤ the upper limit of normal (ULN) with any AST elevation, or total bilirubin 1 to 1.5 times the ULN regardless of AST) as there was no clinically significant difference in PK was between such patients (n = 133) and patients with normal hepatic function.

Only two patients with moderate hepatic impairment were included in the popPK dataset. Patients with total bilirubin > 1.5 times the ULN, ALT or AST > 2.5 times ULN in patients without hepatic metastases and ALT or AST > 5 times ULN in patients with hepatic metastases were excluded from both the pivotal study FRESCO-2 and supportive study FRESCO. The effect of moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN, regardless of AST) on fruquintinib pharmacokinetics is therefore unknown, and safety and efficacy have not been studied adequately in these populations. Additionally, as fruquintinib causes hepatotoxicity, it is not recommended for use in patients with severe hepatic impairment.

No fruquintinib dose adjustment is needed in patients with renal impairment due to its minimal renal excretion.

Interactions

Clinical drug-drug interaction studies were conducted to support instructions for concomitant use. Fruquintinib exposure (area under the concentration time curve (AUC) and C_{max}) is decreased by concomitant administration of strong or moderate CYP3A4 inducers, so these should be avoided during fruquintinib therapy. No dose adjustment is required for mild inducers. Fruquintinib exposure was not meaningfully changed when a strong CYP3A inhibitor was co-administered.

In vitro data suggested fruquintinib might inhibit intestinal P-gp, and intestinal as well as systemic BCRP, at the intended therapeutic dose. In a clinical drug-drug interaction study, co-administration of single oral doses of 5 mg fruquintinib and 150 mg dabigatran (P-gp substrate) showed an approximately 10% decrease in dabigatran exposure across metrics. Co-administration of single oral doses of 5 mg fruquintinib and 10 mg rosuvastatin (BCRP substrate) showed minor impacts on rosuvastatin exposure (14 to 19% across metrics).

Due to the accumulation ratio of approximately 4 for fruquintinib at steady state, a single dose study does not exclude the risk of systemic BCRP inhibition. The sponsor presented physiologically based pharmacokinetic model-based simulations to address this data gap. The overseas regulator conducted additional sensitivity analyses, that indicated that even in a worst-case scenario (maximum dose of fruquintinib, 7-fold reduced inhibition constant (Ki) values and 10-fold increased transporter abundance) the fruquintinib-rosuvastatin drug-drug interaction potential is expected in the range of a mild interaction (49% increase on AUC).

As a result of the above, no dose adjustment is considered necessary for co-administration of fruquintinib with P-gp or BCRP substrates.

Co-administration of proton pump inhibitors or H2 antagonists had no clinically meaningful impact on fruquintinib PK.

Pharmacodynamics

A concentration QT analysis (n = 205 total; 137 in the fruquintinib arm and 68 in the placebo arm) suggested that fruquintinib does not cause > 20 milliseconds increase in mean QTc interval when given at the proposed dosage.[29] QT prolongation at supratherapeutic doses has not been studied.

Safety exposure-response analysis indicated:

- Higher exposure (model-predicted fruquintinib maximum plasma concentration at steady state) was associated with a higher probability of Grade 3 to 4 dermatological toxicity.
- Compared to the daily 3/1 regimen, the daily continuous regimen was associated with higher probabilities of ≥ Grade 3 dermatological toxicity, any grade haemorrhage, and Grade 3 to 4 proteinuria.
- There was no trend of positive exposure-response relationships with fruquintinib or M11 exposure identified for any grade dermatological toxicity, any grade proteinuria, any grade or Grade 3 to 4 hypertension, Grade 3 to 4 hepatic function abnormal, and Grade 3 to 4 haemorrhage.

All patients included in exposure-efficacy analyses received the same dose regimen (5 mg daily 3/1), limiting the breadth of the analysis, which found:

- No trend of a positive relationship between overall survival (OS) and fruquintinib minimum plasma concentration at steady state, whether analysed using the starting dose or adjusted for relative dose intensity, following receipt of the 5 mg once daily 3/1 regimen.
- A (nominally) statistically significant trend of exposure-response relationship between exposure minimum plasma concentration at steady state and progression-free survival (PFS) in Study 2019-013-GLOB1. But given the context of a lack of an exposure-response relationship for OS, this observation may not be clinically meaningful.

Efficacy

Summary of studies contributing to the analysis of efficacy

The efficacy of fruquintinib for the proposed usage was established based on two Phase III studies (described side-by-side in Table 3). FRESCO-2 is the pivotal efficacy study, whilst FRESCO is considered supporting in context of FRESCO-2.

Table 3. Summary of Phase III clinical efficacy studies

Trial ID	Design	Intervention	Endpoints	# enrolled	Population
2019-013-GLOB1 (FRESCO-2)	Randomised, double blind, placebo-controlled, multicenter study conducted globally	(oral) Fruquintinib or matching placebo: 5 mg daily 3/1	Primary: OS Secondary: PFS (key), ORR, DCR, and DOR	Fruquintinib: 461 Placebo: 230	Refractory mCRC

[29] 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.

Trial ID	Design	Intervention	Endpoints	# enrolled	Population
2013-013-00CH1 (FRESCO)	Randomised, double blind, placebo-controlled, multicenter study conducted in China	(oral) Fruquintinib or matching placebo: 5 mg daily 3/1	Primary: OS Secondary: PFS, ORR, DCR, DOR, and duration of SD	Fruquintinib: 278 Placebo: 138	Patients with mCRC who have received at least 2 prior lines of chemotherapy

Abbreviations: # = number, CRC = colorectal cancer, DCR = disease control rate, DOR = duration of response, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, SD = standard deviation.

FRESCO-2 (2019-013-GLOB1)

This was an international, randomised, double blind, placebo-controlled study of fruquintinib plus best supportive care (BSC) versus placebo plus BSC in patients with mCRC who had disease progression on (or were intolerant to) prior treatment with:

- fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy
- an anti-VEGFR biological therapy
- trifluridine/tipiracil (TAS-102) or regorafenib (or both)

Additionally, patients with:

- RAS-wild-type tumours must have received an anti-EGFR therapy
- Tumours that were MSI-h/dMMR must have received an immune checkpoint inhibitor
- Tumours that harbour BRAF V600 mutations must have received treatment with a BRAF inhibitor

As such, the patients enrolled in FRESCO-2 must have received prior therapy in line with what is broadly considered standard-of-care in Australia (see Current treatment options).

Patients must also have been consenting adults (18 years, except 20 years in Japan) weighing at least 40 kg, with ECOG 0-1, measurable disease, left ventricular ejection fraction > 50% on echocardiogram, and adequate organ function by a range of other metrics. Amongst the exclusion criteria were some related to uncontrolled hypertension, risk factors for gastrointestinal ulceration/haemorrhage, particular risk of thromboembolism, baseline QTcF > 480 milliseconds, recent or unhealed surgery, untreated brain metastases, or known human immunodeficiency virus (HIV) infection. Additional detail is provided in the publicly available multi-discipline review.[30]

A total of 691 patients were randomised 2:1 to receive either fruquintinib 5 mg (n = 461), or a matching placebo (n = 230). All patients also received BSC. Randomisation was stratified by:

- Prior therapy with TAS-102 and/or regorafenib (TAS-102 only/regorafenib only/both)
- RAS status (wild type/mutant)
- Duration of metastatic disease (≤ 18 months /> 18 months)

Investigational treatment was given orally, agnostic of recency of food intake, at approximately the same time daily, for the first 21 days of a 28-day cycle (3 weeks on/1 week off or '3/1').

[30] FDA Multi-Discipline Review for FRUZAQLA. Accessed 27 June 2024 at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217564Orig1s000MultidisciplineR.pdf

Treatment continued until disease progression or unacceptable toxicity. The protocol included guidelines for dose modification for specific toxicities including palmar-plantar erythrodysesthesia, proteinuria, hypertension, decreased platelet count, haemorrhage, and abnormal liver function.

Tumour evaluations were conducted every 8 weeks until progression of disease, death, new anti-cancer treatment or study completion.

The primary efficacy outcome was OS, and the key secondary endpoint was PFS by investigator assessment using RECIST v1.1.[31] Other endpoints were not alpha-controlled and included objective response rate (ORR), duration of response (DOR) and patient-reported outcomes for health-related quality of life based on completion of questionnaires.

Assessment of the statistical analysis plan (including censoring rules), protocol amendments, integrity aspects, patient disposition and protocol violations are described in the publicly available multi-discipline review.[30]

FRESCO (2013-013-00CH1)

This study was of a similar design to FRESCO-2 with a few notable differences:

- FRESCO was conducted in a single country (China) rather than across multiple countries.
- FRESCO was earlier than FRESCO-2: starting in December 2014 and ending in January 2017.
- FRESCO enrolled a different population in terms of prior treatments. To participate in FRESCO, patients must have received at least two prior lines of systemic therapy including fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy. Patients had not received prior regorafenib or trifluridine/tipiracil. Patients may have received other agents like anti-VEGF or anti-EGFR monoclonal antibodies, but prior receipt of these drugs was not an inclusion requirement.
- Randomisation in FRESCO was stratified by prior use of VEGF inhibitors (yes versus no) and KRAS gene status (wild type versus mutant).
- Methodology for multiplicity adjustment in testing of secondary endpoints was not clearly specified in the FRESCO study protocol.

Population characteristics for both FRESCO-2 and FRESCO

Baseline demographics, disease characteristics and prior therapies data are presented in Table 4 for both randomised studies. At the time of FRESCO study conduct, regorafenib and trifluridine/tipiracil were not approved in China and it also preceded the use of immune checkpoint inhibitors in patients with MSI-h tumours.

[31] Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47

Table 4: Selected baseline demographics, disease characteristics and prior therapies for the intent-to-treat populations in the FRESCO-2 (pivotal) and FRESCO (supporting) studies

		FRESCO-2 (pivotal)		FRESCO (supporting)	
		Fruquintinib + BSC N = 461	Placebo + BSC N = 230	Fruquintinib + BSC N = 278	Placebo + BSC N = 138
Demographics					
Female sex	%	47	39	43	30
Median (range) age	yrs	64 (25, 82)	64 (30, 86)	55 (23, 75)	57 (24, 74)
Age older than 65y	%	46	48	18	20
ECOG 0	%	43	44	28	27
Region: North America	%	11	10	0	0
Region: Europe	%	71	72	0	0
Region: Asia Pacific	%	18	18	100	100
Baseline disease characteristics					
Left colon primary	%	42	40	77	83
Right colon primary	%	21	23	20	15
Bilateral or unknown colon primary	%	6	7	3	1
Rectal primary	%	31	30	NA	NA
Liver metastases present	%	74	68	67	74
RAS mutant tumour	%	63	63	44	46
BRAF mutation present	%	13	14	NA	NA
MSI-h/dMMR[0]	%	1.1	1.7	NA	NA
MSI-h/dMMR unknown	%	6.3	4.8	NA	NA
Prior therapies					
No prior fluoropyrimidine	n	1	0	0	0
No prior oxaliplatin	n	1	2	0	0
No prior irinotecan	n	2	1	0	0
No prior VEGFR inhibitor	%	3.5	3.9	30	30
RAS & no prior EGFR inhibitor	%	1.8	2.4	75	77
Prior regorafenib only	%	9	8	NA	NA
Prior TAS-102 only	%	52	53	NA	NA
Both regorafenib and TAS-102	%	39	40	NA	NA
No prior regorafenib or TAS-102	%	0	0	100	100

Abbreviations: BRAF = B-Raf proto-oncogene, BSC = best supportive care, dMMR = deficient mismatch repair, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, MSI-h = microsatellite

instability-high, N = number, NA = not assessed/used in this study, RAS = rat sarcoma, TAS-102 = trifluridine/tipiracil, VEGFR = vascular endothelial growth factor receptor, y/yrs = years

[1]Patients in FRESCO-2 with MSI-H/dMMR tumours had all received an immune checkpoint inhibitor previously.

Results for both FRESCO-2 and FRESCO

In the FRESCO-2 study, the addition of Fruzaqla to BSC resulted in a statistically significant improvement in OS and PFS compared to placebo plus BSC. The main results of the FRESCO-2 and FRESCO studies are summarised in Table 5, Figure 2 and Figure 3.

Table 5: Main efficacy findings of the FRESCO-2 (pivotal) and FRESCO (supporting) studies

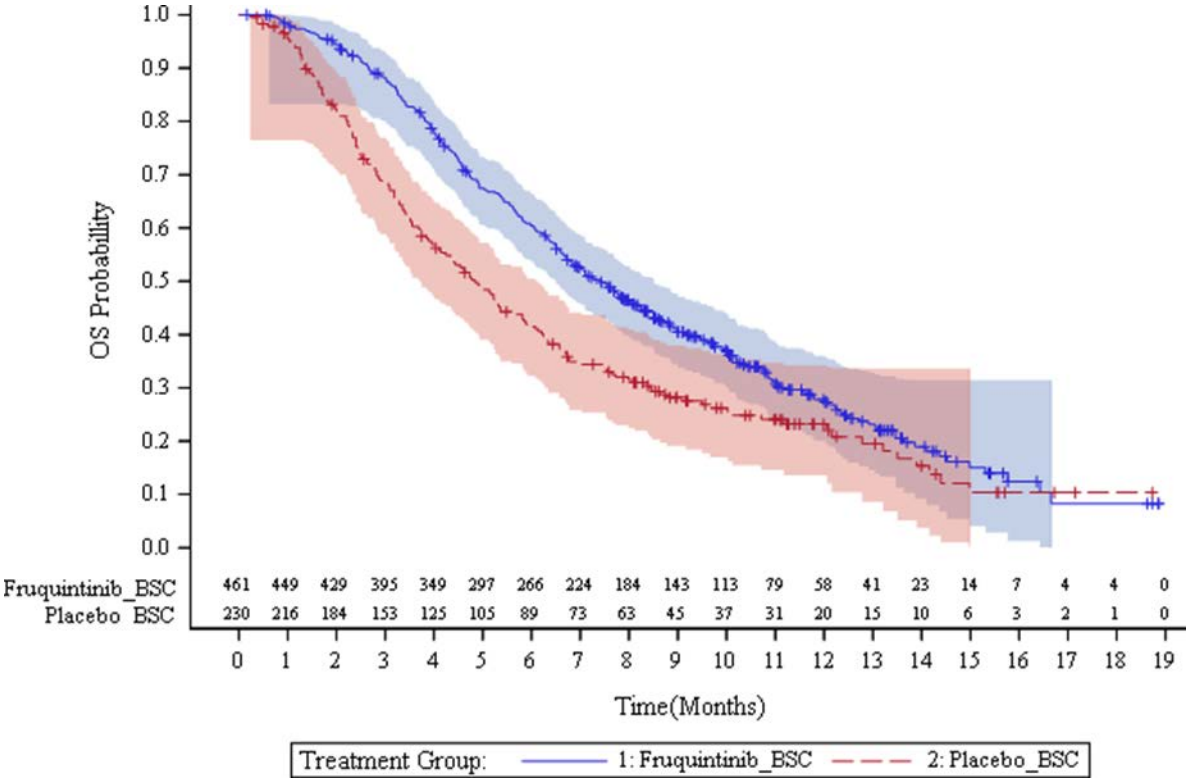
	FRESCO-2 (pivotal)		FRESCO (supporting)	
	Fruquintinib + BSC N = 461	**Placebo + BSC N = 230**	**Fruquintinib + BSC N = 278**	**Placebo + BSC N = 138**
OS				
Number (%) of patients with an OS event	317 (69%)	173 (75%)	188 (68%	109 (79%)
Median OS in months (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)	9.3 (8.2, 10.5)	6.6 (5.9, 8.1)
Adjusted Hazard Ratio[a] (95% CI)	0.66 (0.55, 0.80)		0.65 (0.51, 0.83)	
p-Value[b]	<0.001		<0.001	
PFS				
Number (%) of patients with a PFS event	392 (85%)	213 (93%)	235 (85%)	125 (91%)
Progressions, n (%)	301 (65%)	167 (73%)		
Deaths, n (%)	91 (20%)	46 (20%)		
Median PFS in months (95% CI)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)	3.7 (3.7, 4.6)	1.8 (1.8, 1.8)
Adjusted Hazard Ratio[a] (95% CI)	0.32 (0.27, 0.39)		0.26 (0.21, 0.34)	
p-Value[b]	<0.001		(<0.001; no multiplicity adjustment)	

Abbreviations: BSC = best supportive care, CI = confidence interval, N/n = number, OS = overall survival, PFS = progression-free survival.

[a] Adjusted for stratification factors.

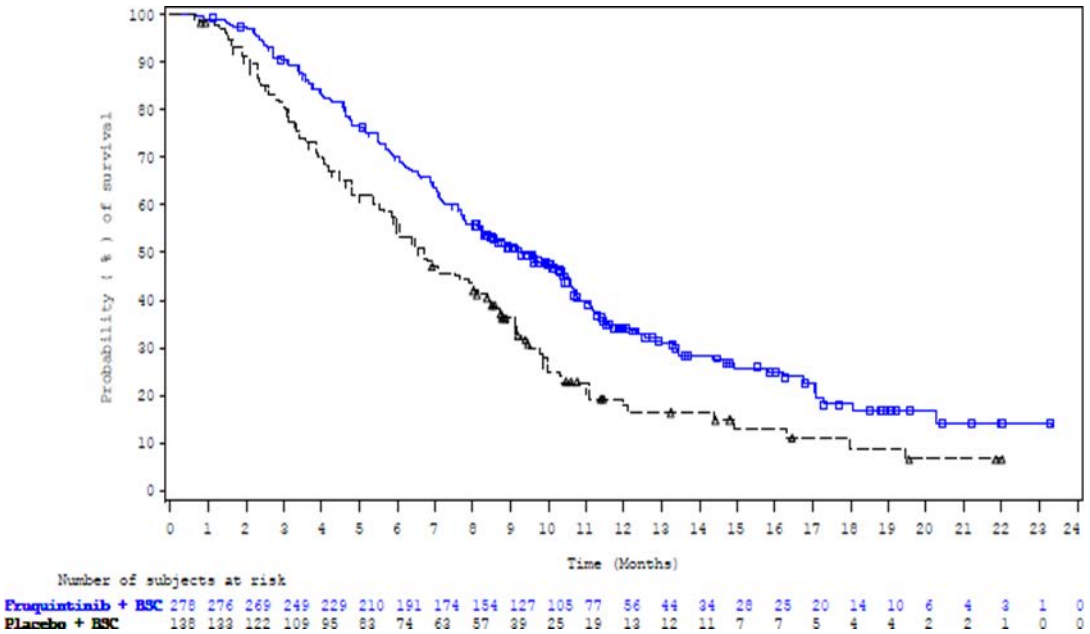
[b] 2-sided p-value computed from stratified log-rank test.

Figure 2: Kaplan-Meier curve for the primary endpoint (overall survival) in FRESCO-2



Abbreviations: BSC = best supportive care, OS = overall survival.

Figure 3. Kaplan-Meier curve for the key secondary endpoint (progression-free survival) in FRESCO



Abbreviations: BSC = best supportive care.

Exploratory subgroup analyses based on a set of pre-specific baseline characteristics did not generate hypotheses of differential efficacy between groups in either study. In subgroups with adequate sample size, the OS results were consistent with the overall results. Amongst 17 patients with a tumour harbouring a BRAF V600E mutation, 7 received fruquintinib, and the hazard ratio for OS was 0.375 (95% confidence interval (CI): 0.089, 1.574). Amongst 9 patients

with known MSI-h/dMMR tumours, 5 received fruquintinib, and the hazard ratio for OS was 0.0.301 (95% CI: 0.016, 5.595).

Crossover from placebo to fruquintinib was not permitted in either trial and review of subsequent therapies did not indicate meaningful imbalances that would be expected to notably influence the primary endpoint of either study.

Among the 691 patients in FRESCO-2, investigator-assessed confirmed ORR was 1.5% (n = 7) in the fruquintinib and BSC arm and 0% in the placebo and BSC arm. All responses were partial. Of the 7 patients who had a response, one died, one had progressive disease, and 5 had not progressed nor died as of the data cut-off date. Among the 416 patients in FRESCO, 13 responses (4.7%) were reported in the fruquintinib arm, and there were zero responses in the placebo arm.

Durability of response to fruquintinib is essentially uninterpretable in either trial due to the very small ORRs, which is in keeping with a cytostatic (rather than cytotoxic) effect. In FRESCO, median DOR was 10.7 months (95% CI: 3.9, not estimable) in the fruquintinib and BSC arm and not estimable for the placebo arm.

Patient-reported outcome completion rates were maintained at around 80% throughout the FRESCO-2 study. Differences were not detected between the placebo arm and the fruquintinib arm in change from Baseline in Quality of Life Core Questionnaire global health status and EuroQol Group 5-dimension 5-level visual analogue scale, however, with significant patient attrition after cycle 3, group sizes became very small (particularly the placebo arm due to the 2:1 randomisation) and confidence intervals were wide and overlapped. The limitations of the data prevent meaningful conclusions. As for ORR and DOR, no alpha control was in place for the patient-reported outcomes analyses in FRESCO-2. Patient-reported outcomes were not measured in FRESCO.

Safety

Summary of studies contributing to the analysis of safety

In addition to FRESCO-2 and FRESCO. the sponsor submitted safety data from:

- a third, smaller randomised study in mCRC (Study 2012-013-00CH1), n = 71; randomised 2:1 (fruquintinib:placebo)
- patients with mCRC who received the recommended dose (5 mg daily 3/1) in single arm studies
- patients with other solid tumours who received the recommended dose (5 mg daily 3/1), including patients with non-small cell lung cancer in randomised Studies 2014-013-00CH1 and 2015-013-00CH1 (FALUCA)
- post-market safety data
- combination studies of fruquintinib

The overseas regulator conducted an in-depth safety review.[30] In addition to the above, the overseas regulator received updated safety results (a '120 day' update). Their review of the update found no substantial change in the safety profile.

This AusPAR focusses on the safety data from FRESCO-2 and FRESCO as they are adequate for characterisation of the safety profile, which was not meaningfully changed by the additional safety data.

Adverse events for the FRESCO study were graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 with adverse events classified and coded using MedDRA version 19.1. Adverse events for the FRESCO-2 study were graded according to NCI-CTCAE version 5.0 with adverse events classified and coded using MedDRA version 25.0.

Data presentations for adverse events (AEs), serious adverse events, AEs leading to discontinuation, and laboratory abnormalities are based on all treated patients using a safety window of 30 days after last dose. Any AEs that began within 30 days post treatment discontinuation but became fatal after this time frame were included in the analysis of fatal events.

Exposure and overall summary of adverse events

The median (range) duration of treatment in weeks was:

- 12 weeks (0 to 82) in the fruquintinib arm and 7 weeks (0 to 51) in the placebo arm in FRESCO-2
- 15 weeks (0 to 95) in the fruquintinib arm and 7 weeks (0 to 48) in the placebo arm in FRESCO

Summaries of the adverse events seen in each study are presented in Table 6.

Table 6: Summary of adverse events across FRESCO-2 and FRESCO

	FRESCO-2		FRESCO	
	Fruquintinib + BSC N = 456 n (%)	Placebo + BSC N = 230 n (%)	Fruquintinib + BSC N = 278 n (%)	Placebo + BSC N = 137 n (%)
All-Grade TEAEs	451 (99)	213 (93)	274 (99)	121 (88)
Grade 3-4 TEAEs	277 (61)	104 (45)	161 (58)	25 (18)
Grade 5	14 (3)	10 (4.3)	7 (3)	2 (1)
SAEs	169 (37)	89 (39)	43 (15)	8 (6)
Patients with AEs leading to treatment interruption	213 (47)	62 (27)	98 (35)	14 (10)
Patients with AEs leading to dose reduction	110 (24)	9 (4)	67 (24)	6 (4)
Patients with AEs leading to treatment discontinuation	93 (20)	49 (21)	41 (15)	7 (5)

Abbreviations: AEs = adverse events, BSC = best supportive care, N/n = number, SAEs = serious adverse events, TEAEs = treatment-emergent adverse events.

Common adverse events and laboratory abnormalities

The most common treatment-emergent adverse events observed with fruquintinib treatment were consistent with those associated with the VEGF tyrosine kinase inhibitor class. The most common adverse events observed in the placebo arm were consistent with the underlying condition. Although more patients in the fruquintinib arm experienced hepatotoxicity, high grade hepatotoxicity occurred with a similar incidence in both arms. The data in FRESCO were not dissimilar.

Table 7: Most common treatment-emergent adverse events in FRESCO-2 (> 10% incidence in the fruquintinib arm)

	Fruquintinib + BSC N = 456; n (%)		Placebo + BSC N = 230; n (%)	
AE	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Fatigue[1]	243 (53.3)	53 (11.6)	89 (38.7)	10 (4.3)
Hypertension[2]	176 (38.6)	65 (14.3)	20 (8.7)	2 (0.9)
Stomatitis[3]	144 (31.6)	11 (2.4)	18 (7.8)	1 (0.4)
Decreased appetite	124 (27.2)	11 (2.4)	41 (17.8)	3 (1.3)
Abdominal pain[4]	115 (25.2)	15 (3.3)	49 (21.3)	7 (3.0)
Diarrhoea[5]	111 (24.3)	17 (3.7)	25 (10.9)	0
Hepatotoxicity[6]	98 (21.5)	32 (7.0)	27 (11.7)	14 (6.1)
Hypothyroidism	94 (20.6)	2 (0.4)	1 (0.4)	0
Palmar-plantar erythrodysaesthesia syndrome	88 (19.3)	29 (6.4)	6 (2.6)	0
Proteinuria[7]	80 (17.5)	8 (1.8)	12 (5.2)	2 (0.9)
Dysphonia[8]	80 (17.5)	0	12 (5.2)	0
Constipation	78 (17.1)	2 (0.4)	22 (9.6)	0
Musculoskeletal pain[9]	75 (16.4)	5 (1.1)	17 (7.4)	0
Vomiting	66 (14.5)	7 (1.5)	26 (11.3)	4 (1.7)
Haemorrhage[10]	61 (13.4)	8 (1.8)	21 (9.1)	4 (1.7)
Weight decreased	56 (12.3)	3 (0.7)	20 (8.7)	1 (0.4)
Thrombocytopenia[11]	55 (12.1)	1 (0.2)	5 (2.2)	1 (0.4)
Back pain[12]	53 (11.6)	6 (1.3)	21 (9.1	4 (1.7)
Arthralgia[13]	51 (11.2)	4 (0.9)	10 (4.3)	0
Pyrexia	46 (10.1)	1 (0.2)	22 (9.6)	0

Abbreviations: AE = adverse event, BSC = best supportive care, N/n = number.

[1] Fatigue is a composite term that includes fatigue and asthaenia.

[2] Hypertension is a composite term that includes hypertension, blood pressure increased, blood pressure diastolic increased, diastolic hypertension, and hypertensive crisis.

[3] Stomatitis is a composite term that includes stomatitis, mucosal inflammation, aphthous ulcer, oral pain, oral dysaesthesia, oral discomfort, glossodynia, glossitis, gingival pain, oropharyngeal pain, oropharyngeal discomfort.

[4] Abdominal pain is a composite term that includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, and hepatic pain.

[5] Diarrhoea is a composite term that includes diarrhoea, colitis, and enteritis.

[6] Hepatotoxicity is a composite term that includes hepatotoxicity, hepatic failure, hepatic cytolysis, hepatic function abnormal, aspartate aminotransferase increased, aspartate aminotransferase abnormal, alanine aminotransferase increased, blood bilirubin increased, bilirubin conjugated increased, hypertransaminasaemia, hyperbilirubinaemia, hepatitis, liver function test increased, and liver function test abnormal.

[7] Proteinuria is a composite term that includes proteinuria, and protein urine present.

[8] Dysphonia is a composite term that includes dysphonia and aphonia.

[9] Musculoskeletal pain is a composite term that includes musculoskeletal pain, musculoskeletal stiffness, myalgia, musculoskeletal chest pain, non-cardiac chest pain, pain in extremity, bone pain, and neck pain.

[10] Haemorrhage is a composite term that includes haemorrhage, conjunctival haemorrhage, eye haemorrhage, gastric haemorrhage, anal haemorrhage, gastrointestinal haemorrhage, hemorrhoidal haemorrhage, upper gastrointestinal haemorrhage, rectal haemorrhage, post-procedural haemorrhage, stoma site haemorrhage, cerebral haemorrhage, vaginal haemorrhage, pulmonary haemorrhage, epistaxis, intermenstrual bleeding, gingival bleeding, haemoptysis, haematochezia, haematemesis, and haematuria.

[11] Thrombocytopenia is a composite term that includes thrombocytopenia and platelet count decreased.

[12] Back pain is a composite term that includes back pain, sacral pain, and spinal pain.

[13] Arthralgia is a composite term that includes arthralgia, arthritis, and arthropathy.

Table 8: Most common laboratory abnormalities worsening from Baseline in FRESCO-2 (> 20% incidence in the fruquintinib arm)

	Fruquintinib + BSC N = 456; n (%)		Placebo + BSC N = 230; n (%)	
AE	**All Grades (%)[1]**	**Grade 3-4 (%)[1]**	**All Grades (%)[1]**	**Grade 3-4 (%)[1]**
Chemistry				
Triglycerides increased	53	2.8	21	1.0
Cholesterol increased	38	2.1	22	1.9
AST increased	36	4.3	24	1.9
Albumin decreased	35	1.6	32	1.4
Sodium decreased	35	1.1	27	0.9
ALT increased	34	5	22	1.4
Bilirubin increased	30	7	21	8
Alkaline phosphatase increased	20	1.6	26	0.5
Magnesium decreased	20	0.5	10	0.5
Haematology				
Lymphocytes decreased	30	6	32	4.6
Platelets decreased	30	0.2	4.6	0
aPTT increased	21	2.7	17	1.5

[1] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Fruzaqla (range: 257 to 277) and placebo (range: 126 to 134).

Fatal adverse events and common serious adverse events

Events with a fatal outcome and those that were considered serious by the investigator were tabulated and described by the overseas regulator.

Fatal event narratives were individually reviewed by TGA and deaths that were considered more plausibly related to fruquintinib than progression of mCRC (based on the available information) are presented in Table 9. Events across both arms were all common causes of mCRC related deaths.

The fruquintinib arms were larger and had a longer time on-treatment than the placebo arm, so direct comparison of rates is confounded. Despite those caveats:

- More fatal infections occurred in patients receiving fruquintinib than those who received placebo.
- There were two fatal events (0.4%) of intestinal perforation amongst patients who received fruquintinib in FRESCO-2, this is an adverse effect that has previously been associated with this class of medication.

Hepatic failure was a cause of death for many patients in the study, in keeping with the underlying condition. One event of fatal hepatic failure occurred within 30 days of ceasing fruquintinib, however the narrative strongly suggests that disease progression could have been responsible. Liver metastases were present at Baseline for this patient, and hyperbilirubinaemia first occurred 169 days after starting treatment. The same day, disease progression (new abdominal cavity and right lung lesions) was present on computed tomography (CT). The narrative goes on to describe 19 days of declining hepatic function, hepatic coma and death, and includes the statement 'the cause of death was reported as disease progression'. This case has not been included in Table 9 (that is, as a fatal AE considered possibly attributable to fruquintinib).

Table 9: Events with a fatal outcome that could not be clearly attributed to disease progression across FRESCO-2 and FRESCO, based on Delegate's clinical review of safety narratives.

	FRESCO-2		FRESCO	
	Fruquintinib + BSC N = 456; n (%)	**Placebo + BSC N = 230; n (%)**	**Fruquintinib + BSC N = 278; n (%)**	**Placebo + BSC N = 137; n (%)**
TOTAL	**8 (1.8)**	**5 (2.2)**	**8 (2.9)**	**5 (1.5)**
Infection[0]	5 (1.1)	1 (0.4)	4 (1.4)	0
Gastrointestinal perforation[0]	2 (0.4)	0	0	0
Pulmonary embolism	1 (0.2)	0	0	0
Haemorrhage[0]	0	0	2 (0.7)	0
Cerebral infarction	0	0	1 (0.4)	0
Sudden death/death of unknown cause/suspected PE	0	2 (0.9)	1 (0.4)	2 (1.4)
Multiple organ dysfunction syndrome	0	1 (0.4)	0	0
Pneumonitis/ILD	0	1 (0.4)	0	0

[1] Infection is a composite term of pneumonia, bacterial infection, COVID-19, and septic shock.

[2] Gastrointestinal perforation is a composite term of intestinal perforation and gastric perforation.

[3] Haemorrhage is a composite term of gastrointestinal haemorrhage and haemoptysis.

The most common serious adverse events across the two Phase III studies are summarised in Table 10.

Table 10: Serious adverse events that occurred in at least 5 patients who received fruquintinib in FRESCO-2 (1% of the investigational arm), or FRESCO (2% of the investigational arm)

	FRESCO-2		FRESCO	
	Fruquintinib + BSC N = 456; n (%)	Placebo + BSC N = 230; n (%)	Fruquintinib + BSC N = 278; n (%)	Placebo + BSC N = 137; n (%)
TOTAL	**157 (34)**	**76 (33)**	**43 (15)**	**7 (5)**
General physical health deterioration	13 (2.9)	7 (3.0)		
Hepatotoxicity[1]	11 (2.4)	6 (2.6)		
Pneumonia[2]	11 (2.4)	1 (0.4)		
Hemorrhage[3]	10 (2.2)	4 (1.7)	6 (2.2)	0
Gastrointestinal perforation[4]	9 (2.0)	0		
Abdominal pain	8 (1.8)	2 (0.9)		
Hypertension[5]	8 (1.8)	0		
Intestinal obstruction	7 (1.5)	7 (3.0)	8 (2.9)	1 (0.7)
Back pain	6 (1.3)	1 (0.4)		
Dyspnoea	6 (1.3)	4 (1.7)		
Pyrexia	6 (1.3)	2 (0.9)		
Urinary tract infection	6 (1.3)	4 (1.7)		
Acute kidney injury	5 (1.1)	1 (0.4)		
Asthenia	5 (1.1)	0		
Pulmonary embolism	5 (1.1)	0		
Sepsis	5 (1.1)	0		
Small intestinal obstruction	5 (1.1)	1 (0.4)		

Source: FDA safety review.[30] Adverse events were presented separately in FDA's analysis for FRESCO-2 and FRESCO. Based on clinical rationale, terms that would likely have been pooled across both FRESCO and FRESCO-2 (if a pooled analysis had been done) have been presented in the same row here for indirect comparison. Cells have been left blank where the term fell below the threshold or was not reported for that study.

[1] Hepatotoxicity is a composite term of blood bilirubin increased, hepatic failure, encephalopathy, hepatic encephalopathy, and hepatic function abnormal.

[2] Pneumonia is a composite term of pneumonia and lung infection.

[3] Haemorrhage is a composite term of cerebral haemorrhage, epistaxis, gastrointestinal haemorrhage, gastric haemorrhage, haematemesis, haematuria, haemoptysis, haemorrhage, intestinal haemorrhage, intermenstrual bleeding, rectal haemorrhage, and upper gastrointestinal haemorrhage.

[4] Gastrointestinal perforation is a composite term of intestinal perforation, small intestinal perforation, gastric perforation, gastrointestinal perforation, large intestine perforation, and rectal perforation.

[5] Hypertension is a composite term of hypertension and hypertensive crisis.

Table 11: Neutropenia based on shift tables of worst change from Baseline for all patients in FRESCO-2

	Fruquintinib + BSC N = 456		Placebo + BSC N = 230	
AE	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
FRESCO-2 neutrophil count decreased, n/N (%)	31/440 (6.8%)	4/440 (9.1%)	4/215 (1.7%)	1/215 (0.5%)
FRESCO neutrophil count decreased, n/N (%)	43/278 (15.5%)	4/137 (2.9%)	2/278 (0.7%)	0/137 (0%)

Abbreviations: BSC = best supportive care, N/n = number.

Dose modifications

Table 12: Adverse events in FRESCO-2 and FRESCO that led to a dose modification (interruption, reduction or discontinuation) above a particular incidence in the investigational arm (blue cells)

Modification type	Interuptions[1]				Reductions[2]				Discontinuations[3]			
Study	**FRESCO-2**		**FRESCO**		**FRESCO-2**		**FRESCO**		**FRESCO-2**		**FRESCO**	
	F	**P**	**F**	**P**	**F**	**P**	**F**	**P**	**F**	**P**	**F**	**P**
TOTAL	**252 (55)**	**66 (29)**	**98 (35)**	**14 (10)**	**110 (24)**	**9 (4)**	**67 (24)**	**6 (4)**	**93 (20)**	**40 (17)**	**41 (15)**	**7 (5)**
Fatigue[4]	33 (7.2)	3 (0.7)			22 (4.8)	3 (1.3)			7 (1.5)	2 (0.9)		
PPES	29 (6.4)	0	19 (6.8)	0	24 (5.2)	0	19 (6.8)	0	3 (0.7)	0		
Proteinuria[5]	26 (5.7)	6 (2.6)	18 (6.5)	1 (0.7)	8 (1.8)	1 (0.4)	16 (5.8)	0	4 (0.9)	0	9 (3.2)	1 (0.7)
Abdominal pain	16 (3.5)	5 (2.2)							3 (0.7)	0		
Vomiting	14 (3.1)	6 (2.6)										
Hypertension	14 (3.1)	1 (0.4)	6 (2.2)	0	17 (3.7)	1 (0.4)	7 (2.5)	0				
Diarrhoea	11 (2.4)	0	6 (2.2)	0	8 (1.8)	0	4 (1.4)	0	3 (0.7)	0		
General physical health deterioration									5 (1.1)	5 (2.2)		
Pulmonary embolism									4 (0.9)	0		
Intestinal obstruction											3 (1.1)	1 (0.7)
Intestinal perforation											2 (0.7)	0
GI perforation[6]									4 (0.9)	0		

Modification type	Interuptions[1]				Reductions[2]				Discontinuations[3]			
Study	FRESCO-2		FRESCO		FRESCO-2		FRESCO		FRESCO-2		FRESCO	
Haemorrhage[7]							3 (1.1)	1 (0.7)	3 (0.7)	1 (0.4)	4 (1.4)	0
Thrombocytopenia[8]			20 (7.2)	1 (0.7)			8 (2.9)	0				
Hepatic fn abnormal											4 (1.4)	0
ALT increased			7 (2.5)	1 (0.7)								
ASP increased							3 (1.1)	0				
Blood Br increased					6 (1.3)	0						

Abbreviations: ALT = alanine aminotransferase, ASP = aspartate aminotransferase, Br = bilirubin, BSC = best supportive care, GI = gastrointestinal, N/n = number, PPES = Palmar-plantar erythrodysaesthesia syndrome.

Source: FDA safety review.[30] Adverse events were presented separately in FDA's analysis for FRESCO-2 and FRESCO. Based on clinical rationale, terms that would likely have been pooled across both FRESCO and FRESCO-2 (if a pooled analysis had been done) have been presented in the same row here for indirect comparison. Cells have been left blank where the term fell below the threshold or was not reported for that study.

[1] Adverse events that led to dose interruption in >2% of patients in the investigational arm.

[2] Adverse events that led to dose reduction in >1% of patients in the investigational arm.

[3] Adverse events that led to permanent discontinuation in >0.5% of patients in the investigational arm.

[4] Fatigue is a composite term that includes asthenia and fatigue.

[5] Proteinuria is a composite term that includes proteinuria and protein urine present.

[6] Gastrointestinal perforation is a composite term that includes gastrointestinal perforation, large intestine perforation, rectal perforation, and small intestinal perforation.

[7] Haemorrhage is a composite term that (pooled across both studies) includes epistaxis, cerebral haemorrhage, gastrointestinal haemorrhage, haematochezia, rectal haemorrhage, upper gastrointestinal haemorrhage, and vaginal haemorrhage.

[8] Thrombocytopenia is a composite term that includes platelet count decreased and thrombocytopenia.

Adverse events of special interest

Adverse events of special interest were nominated by the sponsor based on the known safety profile of other VEGF tyrosine kinase inhibitors, and were hypertension, dermatological toxicity, thyroid dysfunction, proteinuria, haemorrhages, gastrointestinal perforation, infections, embolic and thrombotic events, hepatic function abnormal, left ventricular ejection fraction decreased.

The overseas regulator safety review considered the following expected adverse events of special interest; hypertension, haemorrhage, arterial thrombosis, gastrointestinal perforation, palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome), stomatitis, impaired wound healing, hepatotoxicity, thyroid dysfunction, and proteinuria.

Adverse events of special interest in FRESCO-2 and FRESCO are summarised in Table 13.

Table 13: Adverse events of special interest in FRESCO-2 and FRESCO.

	FRESCO-2				FRESCO			
	Fruquintinib + BSC N = 456; n (%)		Placebo + BSC N = 230; n (%)		Fruquintinib + BSC N = 278; n (%)		Placebo + BSC N = 137; n (%)	
AE	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hypertension[1]	176 (38.6)	65 (14.3)	20 (8.7)	2 (0.9)	170 (61.2)	65 (23.4)	23 (16.8)	3 (2.2)
Stomatitis[2]	142 (31.1)	10 (2.2)	18 (7.8)	1 (0.4)	92 (33.1)	2 (0.7)	4 (2.9)	0
Thyroid dysfunction[3]	135 (27.0)	2 (0.4)	4 (1.7)	0	67 (24.1)	0	9 (6.6)	0
Hepatotoxicity[4]	98 (21.5)	32 (7.0)	27 (11.7)	14 (6.1)	133 (47.8)	21 (7.6)	35 (25.5)	11 (8.0)
Palmar-plantar erythrodysesthesia syndrome	88 (19.3)	29 (6.4)	6 (2.6)	0	137 (49.3)	30 (10.8)	4 (2.9)	0
Proteinuria[5]	80 (17.5)	8 (1.8)	12 (5.2)	2 (0.9)	149 (53.6)	12 (4.3)	39 (28.5)	0
Dysphonia[6]	80 (17.5)	0	12 (5.2)	0	105 (37.8)	0	2 (1.5)	0
Hemorrhage[7]	61 (13.4)	8 (1.8)	21 (9.1)	4 (1.7)	77 (27.7)	5 (1.8)	19 (13.9)	0
Rash[8]	25 (5.5)	0	8 (3.5)	1 (0.4)	25 (9.0)	0	2 (1.5)	0
Gastrointestinal perforation or fistula[9]	16 (3.5)	12 (2.6)	2 (0.9)	2 (0.9)	6 (2.2)	5 (1.8)	1 (0.7)	0
Thrombotic events[10]	17 (3.7)	11 (2.4)	4 (1.7)	1 (0.4)	3 (1.1)	1 (0.4)	1 (0.7)	0
Left ventricular dysfunction[11]	5 (1.1)	3 (0.7)	1 (0.4)	1 (0.4)	3 (1.1)	1 (0.4)	1 (0.7)	0
Wound healing difficulty[12]	1 (0.2)	0	0	0				
Posterior reversible encephalopathy syndrome	1 (0.2)	1 (0.2)	0	0				

[1] Hypertension is a composite term that includes hypertension, pre-hypertension, blood pressure increased, blood pressure diastolic increased, diastolic hypertension, and hypertensive crisis.

[2] Stomatitis is a composite term that includes stomatitis, mucosal inflammation, mouth ulceration, aphthous ulcer, oral mucosal blistering, oral pain, oral dysaesthesia, oral discomfort, glossodynia, glossitis, gingival pain, gingival swelling, gingival ulceration, oropharyngeal pain, oropharyngeal discomfort.

[3] Thyroid dysfunction is a composite term for hypothyroidism, hyperthyroidism, thyroid disorder, thyroxine free decreased, tri-iodothyronine increased, and blood TSH increased.

[4] Hepatotoxicity is a composite term that includes hepatotoxicity, liver injury, hepatic failure, hepatic cytolysis, hepatic function abnormal, hypertransaminasaemia, aspartate aminotransferase increased, aspartate aminotransferase abnormal, alanine aminotransferase increased, alanine aminotransferase abnormal, blood bilirubin increased,

bilirubin conjugated increased, hyperbilirubinaemia, hepatitis, liver function test increased, and liver function test abnormal.

[5] Proteinuria is a composite term that includes proteinuria, and protein urine present.

[6] Dysphonia is a composite term that includes dysphonia and aphonia.

[7] Haemorrhage is a composite term that includes haemorrhage, conjunctival haemorrhage, eye haemorrhage, anal haemorrhage, gastric haemorrhage, anal haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, lower gastrointestinal haemorrhage, haemorrhoidal haemorrhage, haemorrhoid haemorrhage, intestinal haemorrhage, upper gastrointestinal haemorrhage, rectal haemorrhage, post- procedural haemorrhage, stoma site haemorrhage, anastomotic haemorrhage, cerebral haemorrhage, vaginal haemorrhage, pulmonary haemorrhage, epistaxis, intermenstrual bleeding, gingival bleeding, haemoptysis, haematochezia, haematemesis, haemorrhage urinary tract, and haematuria

[8] Rash is a composite term that includes rash, rash erythematous, rash macular, rash maculopapular, and rash pruritis.

[9] Gastrointestinal perforation or fistula is a composite term that includes gastrointestinal perforation, gastric perforation, intestinal perforation, small intestine perforation, large intestine perforation, and rectal perforation.

[10] Thrombotic events is a composite term that includes pulmonary embolism, portal vein thrombosis, device-related thrombosis hepatic vein thrombosis, deep vein thrombosis, venous thrombosis, thrombosis, vena cava thrombosis, cerebrovascular accident, cerebral infarction, pulmonary artery occlusion and acute myocardial infarction.

[11] Left ventricular dysfunction is a composite term that includes cardiac failure, cardiac failure congestive, and left ventricular dysfunction.

[12] Wound healing difficulty is a composite term that includes only the term wound dehiscence.

Lipase and amylase

An additional event of special interest to the TGA Delegate was lipase or amylase elevation. The nonclinical evaluation noted these as a particular potential concern based on nonclinical data. The sponsor provided additional information in the pre-Advisory Committee on Medicines (ACM) Response, including confirmation that lipase was not measured in FRESCO, and an ad-hoc lipase and amylase shift table for FRESCO-2. Whilst no events of Grade 5 were reported, there were two patients (0.4%) with a Grade 4 lipase increase in the fruquintinib arm and one patient with a Grade 4 amylase increase in the fruquintinib arm.

Table 14: Incidence of events and laboratory abnormalities consistent with potential pancreatic toxicity in FRESCO-2 and FRESCO

	FRESCO-2			
	Fruquintinib + BSC % (n/N)		**Placebo + BSC % (n/N)**	
CTCAE grade ->	**Any**	**3+**	**Any**	**3+**
Lipase increase from baseline (laboratory)	16% (43/267)	2.2% (6/267)	8% (9/110)	0.9% (1/110)
Amylase increase from baseline (laboratory)	15% (38/256)	0.4% (1/256)	7% (9/121)	0
Pancreatitis, pancreatitis acute (AE report)	0.7% (3/456)	0.4% (2/456)	0	0
Lipase increased (AE report)	2.4% (11/456)	1.3% (6/456)	0.9% (2/230)	0
Amylase increased (AE report)	2.9% (13/456)	1.1% (5/456)	0.4% (1/230)	0
	FRESCO			

	Fruquintinib + BSC (N total = 278) % (n/N)		Placebo + BSC (N total = 137) % (n/N)	
CTCAE grade ->	**Any**	**3+**	**Any**	**3+**
Amylase increase from baseline (laboratory)	14% (37/265)	2.6% (7/265)	3.7% (5/135)	0
Amylase increased (AE report)	4.3% (12/278)	1.8% (5/278)	0.7% (1/137)	0

Abbreviations: AE = adverse event, BSC = best supportive care, CTCAE = common terminology criteria for adverse events, N = denominator, being the number of patients in the safety set for that arm, and for laboratory shifts, who had a normal baseline, n = number of patients out of the denominator who had a worst post-baseline result in the applicable category of CTCAE Grade (for laboratory shifts), or for whom that AE was reported.
Percentages higher than 5.0% are stated as integers for readability.

Electrocardiograph data

In the FRESCO-2 study, patients with QTcF > 480 milliseconds or any other factors that prolongs the QTc interval or increases the risk of arrhythmic events were excluded from the study.[32] Patients taking medications with a known risk of causing QT prolongation and/or torsade de pointes were also excluded. Electrocardiograph assessments (12-lead) were performed on all patients at Baseline and during Cycles 1 to 3 (C1D1, C1D21, C2D21, and C3D21) using standardised equipment. A continuous 12-lead Holter monitor was used for QTc evaluation during Cycle 1 in a subset of patients. From Cycle 4 onward, electrocardiographs were performed only when clinically indicated.

The overseas regulators interdisciplinary review team for cardiac safety studies conducted a review that concluded that a mean QTc interval prolongation ≥ 20 milliseconds was not observed based on the results of FRESCO-2.

As the QT studies were performed using data from FRESCO-2 rather than a dedicated QT study, the lack of a positive control and the limited exposure margin (as all patients received the same highest dose) prevents a robust conclusion that fruquintinib does not affect QT.

Post-approval safety data

Periodic safety update report (PSUR Version 7.0), representing cumulative post-market data with a data lock point (DLP) of 3 September 2023 (with estimated exposure of more than 92,000 patients) was submitted by the sponsor as part of a response to questions from the ACCESS regulators. This document indicates that cases of posterior reversible encephalopathy syndrome (PRES) and aortic dissection/aneurysm have been reported in the post-market space. In response to a request for more information on such events, the sponsor provided the following information:

> 'Cumulatively, as of 31 January 2024, there are 4 cases of posterior reversible encephalopathy syndrome (PRES) reported in patients treated with fruquintinib. Out of these 4 cases, 3 occurred in the post-marketing setting, and one case was from the FRESCO-2 clinical trial, which had been previously reported in the original application. All 4 events were serious, 3 reported from China and one from Japan. Among the 3 post-marketing cases, 2 were spontaneous post-marketing reports in 2 male patients, both with the event of PRES resolving at the time of the report. The third case was from the literature, occurring in a female patient with the PRES event occurring 10 days after

[32] The **QTcF** is the QT interval corrected for heart rate according to Fridericia's formula.

taking fruquintinib, and with the positive rechallenge. Three of these events were considered related to fruquintinib. For one event, causality could not be clearly evaluated at the time of the report. The event of PRES is currently included as an adverse drug reaction in the proposed Product Information.'

Aortic dissection is not included in the PI as there has been only a single case in the post-market space. However, aneurysms and artery dissections are included in the Risk Management Plan (RMP) as an important potential risk for monitoring.

Real-world evidence

The review was conducted under ACCESS and Project Orbis arrangements. The evaluations did not specify whether real-world data or real-world evidence were included in the submission.[33]

Risk management plan

Takeda Pharmaceuticals Australia Pty Ltd has submitted European Union (EU) RMP version 0.1 (dated 10 May 2023; DLP 24 June 2022) and Australian-specific annex (ASA) version 1.0 (dated 16 August 2023) in support of this application. In its response to questions sent 26 February 2024, the sponsor has submitted EU-RMP version 0.3 (dated 12 March 2024; DLP 24 June 2022) and ASA version 1.1 (dated 19 April 2024) in support of its application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 15. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 15: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Haemorrhage	ü	–	ü	–
	Hypertension	ü	ü*	ü	–
	Posterior reversible encephalopathy syndrome (PRES)	ü	–	ü	–
	Gastrointestinal perforation	ü	–	ü	–
	Palmar-plantar Erythrodysaesthesia Syndrome (PPES)	ü	–	ü	–
	Proteinuria	ü	–	ü	–
Important potential risks	Arterial thromboembolic events	ü	–	ü	–
	Delayed wound healing	ü	–	ü	–
	Aneurysms and artery dissections	ü	–	–	–
Missing information	None	–	–	–	–

[33] Based on FDA definitions, TGA considers real-world evidence (RWE) to be *clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD)*, and RWD to be data derived from sources other than traditional clinical trials, that is. *data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.*

*US Study TAK-113-4002 (ASA only)

The RMP evaluation recommended conditions of registration relating to the versions of the risk management plan, requirement for periodic safety update reports, and inclusion of the medicine in the Black Triangle Scheme.

There are no safety concerns in EU-RMP version 0.3. The safety concerns proposed in the ASA are those adopted by the sponsor as core risks and as per the ACCESS evaluation. 'Dermatologic toxicity' has been changed to 'palmar-plantar erythrodysaesthesia syndrome (PPES)' as an important identified risk. No additional safety concerns have been identified during the ACCESS evaluation.

Routine and additional pharmacovigilance activities are proposed. The proposed additional pharmacovigilance activity (ASA only) is Study TAK-11304002 to be conducted in the US (applicable population). The study was requested by the overseas regulator as a post-market requirement to further characterise the clinical effects of fruquintinib, including pharmacokinetics, activity, blood pressure assessments, and safety events of palmar-plantar erythrodysesthesia in an underrepresented minority population (Black or African American or Other). Study TAK-113-4002 has been added as an additional pharmacovigilance activity. This is acceptable.

Routine risk minimisation activities only are proposed. As fruquintinib is an oral medicine which will be prescribed by specialists, routine risk minimisation activities are sufficient to manage the proposed safety concerns.

The Delegate noted that infection and hepatotoxicity should be added as important identified risks. Pancreatitis should be added as an important potential risk for pharmacovigilance monitoring.

Risk-benefit analysis

Delegate's considerations

Benefits

The FRESCO-2 study was a large, well-designed and appropriately conducted, international, randomised, double blind, placebo-controlled study. Its findings established that for patients with heavily pretreated metastatic colorectal carcinoma, treatment with fruquintinib in the fourth line or later setting is associated with a statistically significant and clinically meaningful improvement in OS compared with placebo.

In FRESCO-2:

- The OS hazard ratio (95% CI) was 0.66 (0.55, 0.80; $p < 0.001$) with a median OS of 7.4 months (6.7, 8.2) in the fruquintinib arm and 4.8 months (4.0, 5.8) for the placebo arm.
- The PFS hazard ratio was 0.32 (0.27, 0.39; $p < 0.001$) with a median PFS of 3.7 months (3.5, 3.8) in the fruquintinib arm and 1.8 months (1.8, 1.9) in the placebo arm.

Whilst the absolute PFS benefit is clinically modest, the statistical significance of the PFS finding supports the robustness of the survival benefit, a finding consistent in sensitivity analyses.

Too few MSI-h/dMMR patients were enrolled to allow meaningful interpretation of efficacy results in that subgroup. However, the Delegate is not aware of any data that would suggest limiting patients with MSS/pMMR tumours.

The FRESCO study was a single country (China), randomised, double blind, placebo-controlled study. It was smaller than FRESCO-2 and enrolled a less heavily pre-treated population. Its findings strongly suggest that for patients with metastatic colorectal carcinoma who have received prior fluoropyrimidine, oxaliplatin-, and irinotecan-based chemotherapy, treatment with fruquintinib in the third line or later setting is associated with a statistically significant and clinically meaningful improvement in OS compared with placebo.

The OS hazard ratio was 0.65 (95% CI: 0.51, 0.83; p < 0.001) with a median OS of 9.3 months (95% CI: 8.2, 10.5) in the fruquintinib arm and 6.6 months (95% CI: 5.9, 8.1) for the placebo arm. The PFS hazard ratio was 0.26 (95% CI: 0.21, 0.34) with a median PFS was 3.7 months (95% CI: 3.7, 4.6) in the fruquintinib arm and 1.8 months (95% CI: 1.8, 1.8) in the placebo arm.

Advice was sought from the ACM as to whether efficacy could be considered adequately established for the proposed usage, which does not align with the population enrolled in FRESCO-2:

> '…who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy.'

This indication does not refer to treatment with TAS-102 or regorafenib, both of which are approved for a similar population to FRESCO. As there was no active comparator in FRESCO-2 (or FRESCO), it is not possible to understand in a statistically robust manner whether treatment with fruquintinib would represent inferior efficacy or safety to the existing registered treatments. If the Delegate was concerned based on exploratory and cross-trial comparisons that fruquintinib was an unacceptable clinical treatment option due to clearly inferior efficacy and safety, it would be difficult for the Delegate to be satisfied that efficacy and safety for the proposed usage had been established.

Efficacy findings across the main fruquintinib, regorafenib and TAS-102 studies are summarised in Table 16.

Table 16: Efficacy findings across the main fruquintinib, regorafenib and TAS-102 studies

STUDY	Treatment arms	Overall survival hazard ratio (95% CI)
FRESCO-2	Fruquintinib v placebo	0.66 (0.55, 0.80)
FRESCO	Fruquintinib v placebo (Asia)	0.65 (0.51, 0.83)
RECOURSE [34]	TAS-102 v placebo	0.68 (0.58, 0.81)
TERRA [35]	TAS-102 v placebo (Asia)	0.79 (0.62, 0.99)
CORRECT [36]	Regorafenib v placebo (global)	0.77 (0.64, 0.94)
CONCUR [37]	Regorafenib v placebo (Asia)	0.55 (0.40, 0.77)

[34] Mayer RJ, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. New England Journal of Medicine. 2015;372(20):1909-19.

[35] Xu J, et al. Results of a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Trifluridine/Tipiracil (TAS-102) Monotherapy in Asian Patients with Previously Treated Metastatic Colorectal Cancer: The TERRA Study. J Clin Oncol. 2018;36(4):350-8.

[36] Grothey A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.

[37] Li J, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2015;16(6):619-29.

In the pre-ACM response, the sponsor provided exploratory analyses and discussion providing justification for considering fruquintinib to be clinically acceptable, despite the lack of an active comparator in clinical studies, for usage in patients who may not have previously received trifluridine/tipiracil or regorafenib, that is, in the current Australian standard-of-care 'third line' mCRC setting. The response included the following:

- The sponsor performed matching-adjusted indirect comparisons between FRESCO and RECOURSE, CONCUR, TERRA, CORRECT, and the control arm of the SUNLIGHT (TAS-102) study.[38] The sponsor states the analysis followed guidelines from the UK National Institute for Health and Care Excellence [39, 40] and used the method of moments to estimate weight parameters.[41] Prior anti-VEGF, prior lines of metastatic disease treatment, age, sex, and ECOG status were treated as effect modifiers. The sponsor concluded that OS was comparable in FRESCO and efficacy was unlikely to be worse with fruquintinib.
- The sponsor described some apparent cross-trial differences in toxicity profile, notably that TAS-102 is commonly associated with severe myelosuppression, while fruquintinib is not. Grade ≥ 3 neutropenia and febrile neutropenia were reported at incidences of 38% and 4%, respectively in RECOURSE. The incidence of Grade ≥ 3 neutropenia was 0.4% and 0% in FRESCO and FRESCO-2, respectively, and no cases of febrile neutropenia occurred.
- The sponsor considered that hepatotoxicity might be less frequently high-grade with fruquintinib than regorafenib, however there is no clear evidence of this.
- The sponsor considered rates of palmar-plantar erythrodysaesthesia syndrome to be possibly different between regorafenib and fruquintinib, however my interpretation of the same data is that incidence of Grade ≥ 3 palmar-plantar erythrodysaesthesia syndrome appeared to be similar with both drugs (10.8% in FRESCO, 6.4% in FRESCO-2, 16.2% in CONCUR and 16.6% in CORRECT).
- Dose form considerations: as an oral therapy, fruquintinib treatment could be feasible in situations where intravenous treatment is not feasible.
- Funding considerations (these are not relevant to TGA considerations).

Considering all of the above, there are not clear reasons for the Delegate to be concerned that fruquintinib represents an unacceptable clinical treatment option that is, a treatment with clearly inferior efficacy or safety to existing standard of care.

With regard to the ability of the dataset to support the requested indication, the ACM's advice is included below.

Risks

The toxicities of fruquintinib are in keeping with those previously described for other members of the VEGF tyrosine kinase inhibitor class, including hypertension, haemorrhage, arterial thrombosis, gastrointestinal perforation, palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome), stomatitis, impaired wound healing, hepatotoxicity, thyroid dysfunction, and proteinuria (see Table 13).

[38] Prager GW, et al. Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med. 2023;388(18):1657-67.

[39] Phillippo D, at al. Methods for Population-Adjusted Indirect Comparisons in Submissions to Nice. Nice DSU Technical Support Document 18. 2016.

[40] Phillippo DM, et al. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. Med Decis Making. 2018;38(2):200-11.

[41] Signorovitch JE, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health. 2012;15(6):940-7.

High-grade (Grade 3 or higher) events that were common in fruquintinib treated but not placebo treated patients were hypertension (14%), palmar-plantar erythrodysaesthesia syndrome (6%), gastrointestinal perforations (3%), stomatitis (2%), proteinuria (2%) and thromboses (2%). Rates of high-grade hepatotoxicity and haemorrhage were similar between the fruquintinib and placebo arms. Palmar-plantar erythrodysaesthesia syndrome is a known effect of small molecules in this class and was among the most common reasons for dose modifications in FRESCO-2 (Table 13).

Analysis of deaths in the study found two cases of gastrointestinal perforation in fruquintinib treated patients, for which disease progression was not clearly causal. Perforation is an adverse event previously described for this class, and the rates of gastrointestinal perforations or fistulas was higher in the fruquintinib than placebo arm (Table 13). More fatal infections (mostly cases of pneumonia) were reported in patients receiving fruquintinib than those who received placebo.

There was one case of Grade 4 PRES in the fruquintinib arm. Three further cases have been reported in post-market data since (with cumulative exposure in approximately 80,000 patients since initial approval; in China in 2018), as well as a single case of aortic dissection.

A greater proportion of patients in the FRESCO study than in the FRESCO-2 study experienced adverse events of special interest. The Delegate agrees with the following comment from the overseas regulator:

> 'Among the most notable differences between the two studies was the difference in the incidence of palmar-plantar erythrodysesthesia syndrome (49% and 19% in FRESCO and FRESCO-2 respectively) in patients treated with fruquintinib arm. The potential role of a more diverse population in the decreased incidence of palmar-plantar erythrodysesthesia in FRESCO-2 cannot be explored with the existing data and the reasons for the difference remain unclear.'

Infections

The RMP evaluation noted that the overseas regulators label contains a warning/precaution regarding infections, as follows, and that no similar warning is included in the proposed Australian PI.

> 'Fruzaqla can cause an increased risk of infections, including fatal infections. In 781 patients treated with Fruzaqla across three randomised, placebo-controlled trials, the overall incidence of infections was higher (18% versus 12%) including for fatal infections (1% versus 0.3%) as compared to the placebo arms (n = 391).'

The sponsor responded to these concerns with the following:

- There is a background risk of infection in patients with advanced-stage malignancies due to compromised immunity.
- The observed higher incidences could be due to a longer duration of exposure/observation. In an integrated safety analysis set composed of all treated patients across FRESCO, FRESCO-2 and an earlier Phase II randomised controlled trial similar to FRESCO:
  - Exposure adjusted incidence of infections was comparable between patients who received fruquintinib (n = 781) and those who received placebo (n = 391) at 4.1 and 4.2 per 100 patient-cycles, respectively.
  - Exposure adjusted incidence of Grade ≥ 3 infections was similar between the two treatment groups: 1.0 and 1.2 per 100 patient-cycles, respectively.

- The median time (Q1, Q3) to onset from first dose was later in fruquintinib treated patients (52 days (17.0, 114)) than placebo patients (31.5 days (13.5, 54.0)).
- The unadjusted incidence of serious infections was comparable between the fruquintinib group and placebo group (4.1% versus 3.3%).
- The incidence of fatal infections was slightly higher than that in the placebo group (1.0% versus 0.3%), but these were mostly attributable to pneumonia which has been included in the product label as an adverse drug reaction.
- There were no incidence increases in other types of serious infections or fatal infections with fruquintinib use compared to placebo.

The Delegate agrees that the rate of infections is likely to be higher in cancer patients, hence the comparison to placebo in a randomised study is the most robust way to assess such effects. The Delegate considers the most relevant dataset to be the FRESCO-2 dataset, which has the clearest external validity to an Australian population. The size of the study is adequate to be reasonably likely to characterise common (incidence > 1%) events.

Vascular endothelial growth factor inhibitors as a class are associated with some myelotoxicity. A number of plausible mechanisms have been proposed.[42] Nonclinical data suggested a potential for haematopoietic toxicity and immunotoxicity of fruquintinib (decreased lymphocytes and atrophy of thymus, atrophy of spleen, mast cell infiltration in the mesenteric lymph nodes).

Of note, neutropenia was more common in patients who received fruquintinib than placebo in FRESCO-2 (Table 11), repeating findings in the earlier FRESCO study. The duration of exposure in both studies was longer in the active compared to the placebo arm, however, this does not account for the increased incidence. Fatal events in both the FRESCO and FRESCO-2 trials indicates an excess of more than double the number of fatal infections in the fruquintinib arms. The sponsor suggests discounting this on the basis that most of the infections were lower respiratory/pneumonias. The Delegate is not aware of any rationale for why pneumonia should be considered separately from other infections and does not believe it is an appropriate approach.

Considering the class of drug and the nonclinical data, as well as the randomised, double blind, placebo-controlled clinical data indicating increased neutropenia and increased rates of serious and fatal infections, the Delegate considers a causal relationship to be clearly plausible.

In response to the above concerns, in the pre-ACM response, the sponsor proposed to include information for infections under 'special warning and precautions for use' in the PI. The Delegate agrees that a warning/precaution is appropriate.

Hepatotoxicity

The PI includes information on dose reductions due to liver function abnormalities but not warning/precaution text.

The approved overseas label includes the following warning text, which the sponsor clarified was requested by the overseas regulator, and is not currently in the Australian PI:

> 'Fruzaqla can cause liver injury. In 911 patients with mCRC treated with Fruzaqla, 48% experienced increased ALT or AST, including Grade ≥ 3 events in 5%, and fatal events in 0.2%. Median time to first onset of elevated liver enzymes was 29 days from first dose of Fruzaqla. Monitor liver function tests (ALT, AST, and bilirubin) before initiation and

[42] Schmidinger M. Understanding and managing toxicities of vascular endothelial growth factor (VEGF) inhibitors. EJC Suppl. 2013 Sep;11(2):172-91.

periodically throughout treatment with Fruzaqla. Temporarily hold and then reduce or permanently discontinue Fruzaqla depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests [see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].'

In response to this concern, the sponsor stated that in FRESCO-2, the number of Grade ≥ 3 events, serious adverse events and fatal events were comparable to placebo and liver function test abnormalities infrequently led to dose reduction, interruption, or treatment discontinuation. The sponsor therefore concludes that fruquintinib is not associated with an increased risk of severe or serious liver function abnormalities. The sponsor considers that as this population would routinely receive liver function monitoring (most patients have or will have liver metastases), a warning on hepatotoxicity in the label is not necessary.

The Delegate agrees with the pragmatism reflected in the latter part of the sponsor's proposal but is unconvinced that the data demonstrate fruquintinib is not associated with an increased risk of severe or serious liver injury. Such events are not common, so increased risk of severe or serious liver injury is difficult to assess in a population the size of the submitted dataset.

One case of fatal hepatic failure occurred within 30 days of ceasing treatment in the fruquintinib arm of FRESCO-2 but may have been attributable to disease progression based on narrative review.

As for infections, pooling across studies may not assist in delineating effects in the most relevant population and could mask real drug effects. The submitted nonclinical and clinical data (AE data and laboratory shift data) indicate that, probably, fruquintinib commonly causes mild hepatotoxicity. Fruquintinib has not been studied in patients with moderate or severe hepatic impairment, and it is plausible that such populations would experience additive or synergistic hepatotoxicity.

In response to the above concerns, in the pre-ACM response, the sponsor proposed to add information regarding hepatotoxicity to 'special warnings and precautions for use' and 'adverse effects (undesirable effects)'. The Delegate agreed with the addition of PI text regarding hepatotoxicity.

Dose advice in moderate hepatic impairment

An issue related tangentially to hepatotoxicity is dose recommendations for patients with existing moderate hepatic impairment. The sponsor has proposed no dose adjustment, based on a dedicated hepatic impairment PK study (Study 2021-013-00US1) in which PK for fruquintinib and M11 was similar amongst 8 patients with moderate hepatic impairment based on Child Pugh score (Child Pugh B), compared to historical PK data from healthy subjects.

It is unclear whether this PK data is robust enough to support a conclusion of similar PK, as 7 of the patients with Child Pugh B scores had mild impairment or normal liver function when scored according to an alternative major scoring system.

Regardless of PK, safety concerns remain. It is plausible that fruquintinib related deterioration in hepatic function could cause decompensation or complications in patients who start treatment with a baseline of moderate hepatic impairment. Inadequate numbers of patients with moderate hepatic impairment (n = 2) or severe hepatic impairment (n = 0) were enrolled in the pivotal trials FRESCO-2 and FRESCO, and mCRC patients with liver cirrhosis or fibrosis were excluded from enrolment. Therefore, there is inadequate PK or safety data to support a dose recommendation for treatment of patients with moderate hepatic impairment.

Pancreatic enzyme elevation

Nonclinical data indicated the need to assess the clinical trial data for potential pancreatic toxicity. The data (Table 14) indicates a difference between arms that is consistent across the two independent randomised studies. Fruquintinib appears to cause pancreatic enzyme elevation clinically in around 10 to 15% of patients. Whilst this is low grade for most cases, these are clinically relevant for a small proportion of patients (perhaps 1 to 2%). Adverse events of pancreatitis were not notably imbalanced between arms, but with the size of the dataset, it is possible that this partly reflects chance. Whilst the Delegate doesn't believe the data support addition of a warning relating to pancreatitis, the Delegate does propose addition of specific information to the PI in section 4.8 describing the data seen in the trials. The Delegate would also like the sponsor to consider adding pancreatitis to the RMP as an important potential risk for pharmacovigilance monitoring.

Allergy to azo dyes

The approved overseas label contains a specific warning regarding allergy to azo dyes as follows:

> 'Fruzaqla 1 mg capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.'

The sponsor proposes that the existing statement in the contraindications section of the Australian PI ('hypersensitivity to the active substance or any of the excipients listed in section 6.1') adequately informs prescribers and patients about potential hypersensitivity or allergic reactions to the excipient.

The excipients section of the Australian PI will be reviewed for clarity, but in general the Delegate agrees with the sponsor's proposed approach. There are no other products the Delegate is aware of for which the Australian PI contains specific text in warnings and precautions regarding potential for allergy to an excipient. In general, the approach is that the contraindications section acts as a reminder to check excipients if a person has a known allergy.

Proposed action

Noting the pre-treated population and severity of this condition, the demonstrated efficacy findings of fruquintinib for pre-treated mCRC are both statistically significant and clinically meaningful, though they are modest in terms of absolute PFS and OS gain.

The FRESCO study alone would be insufficient to support Australian registration with an indication that did not require prior use of regorafenib or TAS-102, because it is a single country study conducted against a comparator (placebo) that is now outdated for Australian patients. However, it is contextualised by the very similar findings of FRESCO-2 which is a more contemporary study in an international population with a similar standard-of-care to current Australian treatment. There is no reason to expect that the efficacy or safety or fruquintinib should be contingent on prior use of either regorafenib or TAS-102.

The Delegate therefore proposes to approve the registration of fruquintinib in Australia for essentially the requested indication. The advice of the ACM committee supports this approach with regard to the indication wording, which is also aligned with the approach taken by the overseas regulator.

Infection and hepatotoxicity should be added as an important identified risks to the RMP, and pancreatitis should be added as an important potential risk for pharmacovigilance monitoring.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***Noting the lack of any comparison to active therapy, are the study designs of FRESCO and FRESCO-2 adequate to support a full assessment of the safety and efficacy of fruquintinib for the proposed earlier line usage ('third line' or later treatment of metastatic colorectal cancer in Australia), rather than just for a later line usage, in keeping with the study population of FRESCO-2?***

The ACM was of the view that outcomes of the FRESCO and FRESCO 2 are sufficient to support a full assessment of the safety and efficacy of fruquintinib.

The ACM noted that the trial population of the FRESCO 2 study is the most relevant to Australian clinical practice, which would support aligning the indication with the more restrictive indication registered in the EU.

However, the ACM agreed that the more permissive indication registered by the US could be reasonable when considering the results of both trials together, and from a practical perspective, clinicians would have few concerns about initiating fruquintinib in patients who had not previously been treated with regorafenib or TAS 102 if it was clinically warranted.

Conclusion

Noting that this request is for early advice, based on currently available evidence the ACM considered this product to have an overall positive benefit-risk profile. Alignment with the US indication is preferred.

Outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Fruzaqla (fruquintinib) 1 mg and 5 mg, hard capsule, bottle, indicated for:

> *Fruzaqla is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF agent, and an anti-EGFR agent if appropriate.*

Specific conditions of registration applying to these goods

- Fruzaqla (fruquintinib) is to be included in the Black Triangle Scheme. The PI and CMI for Fruzaqla must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.
- The Fruzaqla EU-Risk Management Plan (RMP) (version 0.3, dated 12 March 2024, data lock point 24 June 2022), with Australian Specific Annex (version 1.1 dated 19 April 2024),

included with submission PM-2023-04088-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

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 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. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six-monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates 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.

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 be submitted within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The Product Information (PI) approved with the submission for Fruzaqla which is described in this AusPAR can be found as Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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Reference/Publication #