Single Technology Appraisal

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Takeda UK:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Bowel Cancer UK

4. **Expert personal perspectives** from:
   a. Harpreet Singh Wasan– clinical expert, nominated by Takeda UK

5. **External Assessment Report** prepared by Aberdeen HTA group

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Document B
Company evidence submission

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Abbreviations

Abbreviation	Definition
ACJJ	American Joint Committee on Cancer
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criteria
AFT	Accelerated failure time
ASCO	American Society of Clinical Oncology
AUC	Area-under-the-curve
BIC	Bayesian information criteria
BNF	British National Formulary
BOR	Best overall response
BRAF	V-raf murine sarcoma viral oncogene homologue B
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CI	Confidence interval
CR	Complete response
CRC	Colorectal cancer
CrI	Credible interval
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
EAG	External assessment group
ECOG PS	Eastern Cooperative Oncology Group performance status
EEPRU	Economic Evaluation of Health and Care Interventions
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L	EuroQol five-dimension three-level
EQ-5D-5L	EuroQol five-dimension five-level
ESMO	European Society for Medical Oncology
FE	Fixed effects
FGFR	Fibroblast growth factor receptor
FOLFIRI	Folinic acid, fluorouracil and irinotecan
FOLFOX	Folinic acid, fluorouracil and oxaliplatin
FOLFOXIRI	Folinic acid, fluorouracil, oxaliplatin and irinotecan
G-CSF	Granulocyte colony-stimulating factor
GP	General practitioner
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison

ITT	Intention-to-treat
KIT	KIT proto-oncogene receptor tyrosine kinase
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homologue
LSM	Least squares mean
LVEF	Left ventricular ejection fraction
MC	Monte Carlo
mCRC	Metastatic colorectal cancer
MMR	Mismatch repair
MOA	Mechanism of action
MRU	Medical resource use
MSI-H	Microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NTRK	Neurotrophic tyrosine receptor kinase
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD	Progressive disease
PD-1	Programmed cell death protein 1
PDGFR	Platelet-derived growth factor receptor-like protein
PFS	Progression-free survival
PH	Proportional hazards
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once a day
QLQ-C30	Core Quality of Life questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Proto-oncogene tyrosine-protein kinase receptor Ret
RWD	Real world data
RWE	Real world evidence
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor

TNM	Tumour node metastasis
TTD	Time to treatment discontinuation
TTO	Time trade-off
UK	United Kingdom
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WTP	Willingness-to-pay
XELOX	Oxaliplatin and capecitabine

B.1 Decision problem, description of the technology and clinical care pathway

Colorectal cancer (CRC) is the third most common type of cancer in the United Kingdom (UK), and the second most common cause of cancer-related deaths (1)

- CRC is a heterogeneous group of diseases with distinctive genetic and epigenetic backgrounds (2). There are around 42,900 new cases of CRC each year in the UK, accounting for 11% of all new cancer diagnoses, and 16,800 deaths due to CRC (10% of all cancer-related deaths) (3)
- Approximately 90% of CRCs are adenocarcinomas derived from epithelial cells of the colorectal mucosa (2)
- Patients with CRC may present with changes in bowel habit, rectal bleeding, weight loss, and anaemia (4)
- Following diagnosis, the tumour will be staged, most often using the American Joint Committee on Cancer (ACJJ) tumour node metastasis (TNM) classification system, where disease stage ranges from Stage 0 in situ disease to Stage IV metastatic disease (5)

Metastatic colorectal cancer (mCRC) is associated with markedly worse clinical outcomes than early stage disease and with significant humanistic and economic burden

- In England, approximately 22% of newly diagnosed patients with CRC are diagnosed with metastatic (Stage IV) disease (6). Additionally, approximately 55% of patients with Stage II and Stage III disease will go on to develop metastases (7)
- Despite good survival outcomes for patients with early stage CRC, metastatic disease is associated with poor clinical outcomes, with a 5-year survival rate of 10.5%, compared with 90.9% for patients with Stage I disease (6). Patients newly diagnosed with mCRC may achieve a median overall survival (OS) of 30 months with treatment (8). However, treatment benefit diminishes with each additional therapy received; in patients who have received two or more previous lines of treatment, median OS decreases to around only 5–7 months (9, 10)
- For patients with mCRC who have failed prior chemotherapy and biological therapy, the only National Institute for Health and Care Excellence (NICE)-approved treatment options are trifluridine-tipiracil and regorafenib, but these are associated with toxicities that can negatively impact health-related quality of life (HRQoL), such as myelosuppression, fatigue, and hand-foot syndrome (9-11), and can also affect patients' ability to receive further treatment (12). This highlights a substantial unmet need for patients with mCRC who require alternative options, and an unmet need for patients who have been previously treated with or are not considered candidates for available therapies, and for whom the only remaining option is best supportive care (BSC)
- mCRC has a substantial impact on patient HRQoL due to burdensome symptoms such as fatigue, nausea, altered bowel habits, abdominal pain, rectal bleeding, and microcytic anaemia (13). Furthermore, HRQoL decreases with each additional therapy received (14) and therefore, the main aims of treatment in the previously-

treated setting are to prolong survival while maintaining the best possible HRQoL (15)
- CRC imposes a significant economic burden on healthcare systems, with the cost of treating CRC in the UK estimated at over £1.7 billion a year (16, 17)

Fruquintinib is a highly selective, potent inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinases, and would offer an alternative treatment option for patients with previously treated mCRC

- Fruquintinib targets all three VEGFRs, but has minimal inhibitory effect on other kinases, and therefore offers a highly selective mechanism of action (MOA), compared with other VEGF/VEGFR inhibitors currently used in mCRC (18, 19). This high selectivity is expected to minimise off-target toxicity, which is thought to contribute to the favourable safety profile of fruquintinib (18)
- By blocking signalling through the VEGF pathway, fruquintinib suppresses angiogenesis, restricting tumour progression. Additionally, by suppressing VEGFR-3, fruquintinib has the potential to inhibit lymphangiogenesis (18, 19)
- Fruquintinib is anticipated to be indicated for the treatment of [redacted]
- Fruquintinib provides selective target coverage to address the high unmet need of patients who have been previously treated with or are not considered candidates for available therapies, and is taken through a convenient, oral, once-daily mode of administration

B.1.1 Decision problem

The submission covers the technology's full anticipated marketing authorisation for this indication.

The decision problem addressed in this submission is provided in Table 1, which outlines any differences from the NICE final scope (20).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with metastatic colorectal cancer (mCRC) who have had two or more previous treatments	[redacted]	The population is aligned with the anticipated licensed indication (21)
Intervention	Fruquintinib	As per final scope	–
Comparator(s)	• Trifluridine-tipiracil monotherapy • Regorafenib • Best supportive care	As per final scope	–
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per final scope	–

Abbreviations: EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; mCRC, metastatic colorectal cancer; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; VEGF, vascular endothelial growth factor.

B.1.2 Description of the technology being evaluated

The technology being appraised in this submission (fruquintinib) is described in Table 2. The draft summary of product characteristics (SmPC) is provided in Appendix C.

Table 2: Technology being evaluated

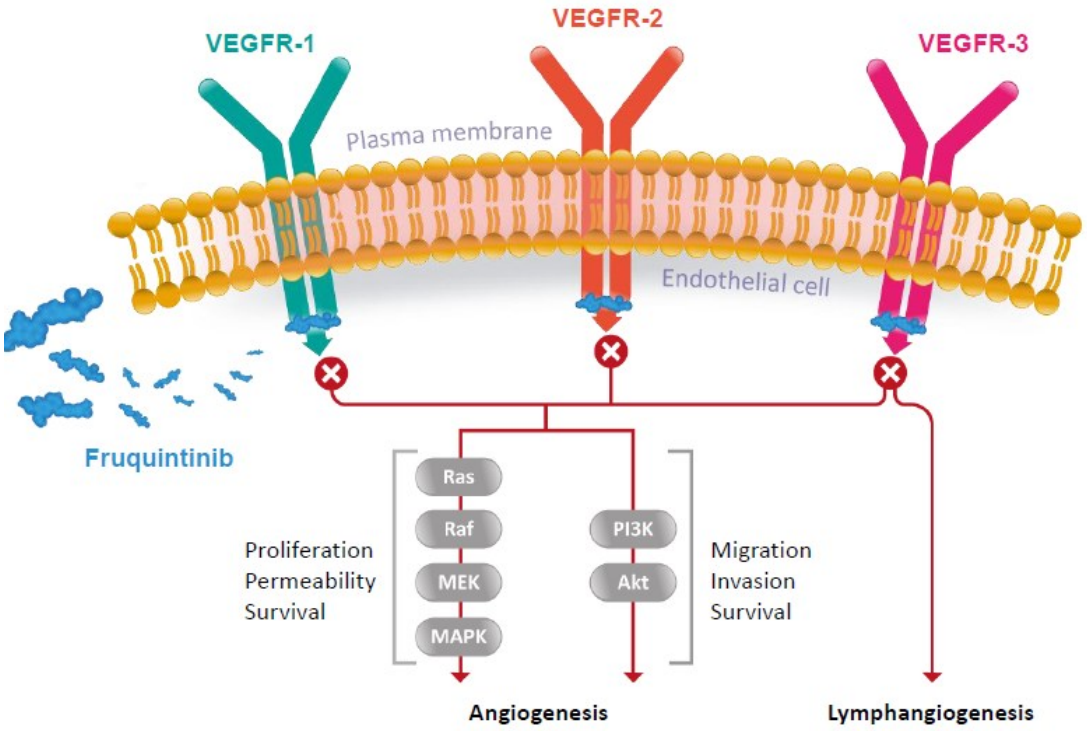
UK approved name and brand name	Fruquintinib (Fruzaqla™)
Mechanism of action	Fruquintinib is a highly selective and potent oral inhibitor of VEGFR -1, -2 and -3 tyrosine kinases (18). The cytokine VEGF is crucial for angiogenesis, and targeting the VEGF pathway is a well-accepted anti-cancer strategy, since tumour growth and metastases depend on development of new blood vessels (22). By blocking signalling through the VEGF pathway, fruquintinib suppresses angiogenesis and prevents tumour progression. Additionally, fruquintinib has the potential to inhibit lymphangiogenesis via suppression of VEGFR-3 (16, 17). By targeting all three VEGFRs while having minimal inhibitory effect on other kinases, fruquintinib offers a highly selective MOA, compared with other VEGF/VEGFR inhibitors currently used in mCRC† (18, 19)
Marketing authorisation/CE mark status	A regulatory submission was made to the MHRA, via the Access Consortium, on [redacted], with approval expected in [redacted]. Fruquintinib has been granted an innovation passport as part of the Innovative Licensing and Access Pathway (ILAP/IP/23/16189/02) Fruquintinib was granted a Priority Review designation and was subsequently approved by the FDA on 8th November 2023 via Project Orbis (23)
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	[redacted]
Method of administration and dosage	The recommended dose of fruquintinib is 5 mg (one 5 mg capsule) QD at approximately the same time each day for 21 consecutive days, followed by a 7 day rest period to comprise a complete cycle of 28 days. Fruquintinib is available as 1 mg and 5 mg capsules Dose adjustments for adverse reactions: the dose should be modified based on safety and tolerability. First dose reduction to 4 mg QD; second dose reduction to 3 mg QD. Fruquintinib should be permanently discontinued in patients unable to tolerate a dose of 3 mg QD. Treatment with fruquintinib should be continued until disease progression or unacceptable toxicity occurs
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment‡	List price for 5 mg tablets: £[redacted] per pack of 21 tablets List price for 1 mg tablets: £[redacted] per pack of 21 tablets Average cost for a course of treatment (based on mean duration of treatment from the economic model of [redacted] months): £[redacted].

Patient access scheme (if applicable)¶	Fruquintinib will be available via a proposed simple PAS, offering a discount of [redacted]% off the list price, which has been applied to the below: PAS price for 5 mg tablets: £[redacted] per pack of 21 tablets PAS price for 1 mg tablets: £[redacted] per pack of 21 tablets Average cost for a course of treatment (based on duration of treatment from the economic model of [redacted] months): £[redacted].

†Anti-VEGF agents such as bevacizumab neutralise VEGF while anti-VEGFR agents such as fruquintinib and regorafenib inhibit VEGFR kinase activity; ‡A proposed list price has been submitted to Department of Health and Social Care, and is currently undergoing consideration; ¶A proposed [redacted] PAS has been submitted to PASLU, and is currently undergoing consideration.
Abbreviations: EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; ILAP, Innovative Licensing and Access Pathway; mCRC, metastatic colorectal cancer; MHRA, Medicines and Healthcare products Regulatory Agency; MOA, mechanism of action; NHS, National Health Service; PAS, patient access scheme; PASLU, Patient Access Schemes Liaison Unit; QD, once daily; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Fruquintinib is a highly selective and potent oral tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR) (18). By targeting all three VEGFRs while having minimal inhibitory effect on other kinases, fruquintinib offers a highly selective mechanism of action (MOA), compared with other current VEGF/VEGFR inhibitors used in metastatic colorectal cancer (mCRC) (18, 19). This high selectivity for VEGFRs is expected to minimise off-target toxicity, allowing for high drug exposure and sustained target inhibition. By blocking signalling through the VEGF pathway, fruquintinib suppresses angiogenesis and prevents tumour progression (Figure 1). Additionally, fruquintinib has the potential to inhibit lymphangiogenesis via suppression of VEGFR-3 (16, 17). Fruquintinib was designed to improve kinase targeting and selectivity, to improve tolerability and support longer duration of therapy. Overall, fruquintinib provides consistent and selective target coverage to address the unmet need and tolerability challenges posed by currently available treatments for previously treated mCRC (18, 19).

Figure 1: Fruquintinib-mediated inhibition of VEGFRs



Source: Geindreau et al, 2021 (24), Qin et al, 2019 (25) Zhang et al, 2019 (19).
Abbreviations: Akt, protein kinase B; MAPK, mitogen activated protein kinase; MEK, mitogen activated protein kinase kinase; PI3K, phosphoinositide 3 kinase; Raf, rapidly accelerated fibrosarcoma; Ras, rat sarcoma virus; VEGFR, vascular endothelial growth factor receptor.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Colorectal cancer (CRC) is a heterogeneous group of diseases with distinctive genetic and epigenetic backgrounds (2). About 66% of new CRCs arise in the colon (43% in the proximal colon and 23% in the distal colon), and approximately 30%[1] occur in the rectum (26). Around 90% of CRCs are adenocarcinomas derived from epithelial cells of the colorectal mucosa. The vast majority of colorectal adenocarcinomas derive from precursor lesions such as adenomas, serrated polyps, and dysplasia (2).

Molecular pathways have been implicated in the development of CRC, including chromosomal instability (observed in 65–70% of sporadic colorectal tumours) and microsatellite instability, which is caused by defects in the deoxyribonucleic acid (DNA) mismatch repair (MMR) system and accounts for approximately 15% of tumours (27, 28).

[1] The remaining 4% are classified as either “Other site-overlapping lesion of colon” or “Colon, not otherwise specified”.

Additionally, alterations in individual genes such as Kirsten rat sarcoma viral oncogene homologue (*KRAS)*, v-raf murine sarcoma viral oncogene homologue B (*BRAF)* and human epidermal growth factor receptor 2 (*HER2*) occur in approximately 44%, 10%, and 3–5% of mCRC cases, respectively (29, 30). Although rare (<1%), neurotrophic tyrosine receptor kinase (*NTRK*) fusion-positive tumours are believed to represent a unique subset of CRC, with a high tumour mutational burden and are likely to be microsatellite-unstable (31). All these genetic alterations may impact on the therapy patients with metastatic disease receive in early lines of treatment (Section B.1.3.4.1).

Patients with CRC may present with changes in bowel habit, rectal bleeding, weight loss, and anaemia (4). For symptomatic patients, or those with an abnormal screening test, a diagnosis of CRC will be made based on results from stool tests, blood tests, diagnostic colonoscopy or proctoscopy, and biopsy (32). Following diagnosis, the tumour will be staged: in the UK, most clinicians will use the American Joint Committee on Cancer (ACJJ) tumour node metastasis (TNM) classification system (Table 3) (5, 33).

In Stage IV CRC (henceforth referred to as mCRC), the primary tumour has metastasised to distant organs or distant parts of the peritoneum (Table 3). The liver is recognised as the most common site of metastasis in mCRC, with more than 50% of patients with CRC developing liver metastases, either as synchronous or metachronous disease. This ultimately results in death for more than two thirds of these patients (34). Between 15% and 25% of patients presenting with mCRC have synchronous liver metastases (35).

Table 3: ACJJ tumour staging of CRC

Stage	Description
0	The tumour is in situ (Tis, N0, M0)
I	• The primary tumour has grown into the submucosa (T1) or the muscle (T2) • No nodal involvement, no distant metastases (N0, M0)
II	• The primary tumour has grown into the outermost layers of the colon (T3) or • has grown through the wall of the colon or rectum (T4a) or • has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organ (T4b) • No nodal involvement, no distant metastases (N0, M0)
III	• T1 or T2 tumour which has spread to 1 to 3 nearby lymph nodes (N1a and N1b) or into areas of fat near the lymph nodes but not the nodes themselves (N1c) or to 4–6 regional lymph nodes (N2a) or ≥7 regional lymph nodes (N2b) or • T2 or T3 tumour with nodal involvement N2a or • T3 or T4a tumour with nodal involvement N1a–N1c or • T4b tumour with nodal involvement N1 or N2 • The tumour has not spread to distant sites (M0)
IV	• The primary tumour may or may not have grown through the wall of the colon or rectum (Any T). It may or may not have spread to regional lymph nodes (Any N) • The tumour has spread to 1 distant organ or distant set of lymph nodes, but not to distant parts of the peritoneum (M1a) or • It has spread to more than 1 distant organ (such as the liver or lung) or distant set of lymph nodes, but not to distant parts of the peritoneum (M1b) or • It has spread to distant parts of the peritoneum, and may or may not have spread to distant organs or lymph nodes (M1c)

Source: American Cancer Society (5)
Abbreviations: ACJJ, American Joint Committee on Cancer; CRC, colorectal cancer.

B.1.3.2 Epidemiology

In the UK, CRC is the third most commonly diagnosed cancer (1). There are around 42,900 new cases of colorectal cancer each year in the UK, accounting for 11% of all new cancer diagnoses (3); of those new CRC cases, in 2020, 34,405 were diagnosed in England (36). In 2020, 7,684 patients were diagnosed with Stage IV mCRC in England, accounting for 22.3% of all CRC cases in England. In addition, a total of 16,624 patients were diagnosed with Stage II and III CRC in England (21.7% and 26.6% of all CRC cases in England, respectively) (6), and it is estimated that 55% of these patients will go on to develop metastases (7). Therefore, it is estimated that around 16,800 new cases of mCRC are

diagnosed in England each year, of which an estimated 20-25% will go on to reach the third-line or beyond setting (7), although this figure is likely to be lower outside of tertiary cancer centres (11).

Risk factors for developing CRC include:

- Age: In the UK, 94% of all new CRC cases are diagnosed in people aged 50 years and over, with incidence rates at their highest in people aged 85–89 years (3, 37) . It must be noted, however, that incidence rates are increasing in younger people, with the most sustained increase seen in the 20–29 years age group (38)
- Sex: CRC is more prevalent in men than women (56% vs 44%) (1, 3)
- Family history (39)
- Lifestyle factors such as smoking, high consumption of red and processed meat, obesity, diabetes, and excessive consumption of alcohol (39).

B.1.3.3 Disease burden

B.1.3.3.1 Clinical burden

Globally and in the UK, CRC is the second most common cause of cancer-related deaths (1). In England, a bowel cancer screening programme means a screening test is automatically sent to people who are aged 60–74 years and registered with a general practitioner (GP), every 2 years (4, 40), which aims to identify CRC cases at the earliest stage possible. Despite this, 48.9% of all patients with CRC in England are diagnosed with Stage III or Stage IV disease (6).

Long-term survival varies depending on disease stage at diagnosis and worsens considerably if patients present with, or develop, metastatic disease. In England, the 1-year survival rate is 97.9% for patients diagnosed with Stage I CRC, but only 43.6% for Stage IV disease, and the 5-year survival rate decreases dramatically from 90.9% for Stage I CRC to just 10.5% for Stage IV disease (6).

Median overall survival (OS) for patients with newly diagnosed mCRC is 30 months when treated in alignment with the European Society for Medical Oncology (ESMO) guidelines[2] (8), but this reduces with each line of failed therapy. In patients who have received two or more previous lines of treatment, median OS is only 5.0–7.7 months (9, 10, 15, 41). Similarly, median progression-free survival (PFS) for patients receiving first-line treatment is 8.5 months, decreasing to just 1.9–3.3 months for patients who have received two or more lines of therapy (the target population for fruquintinib) (9, 10, 42-45).

Patients with mCRC experience burdensome symptoms such as fatigue, nausea, altered bowel habits, abdominal pain, rectal bleeding, and microcytic anaemia (13). Patients with liver metastases may also experience jaundice and ascites (46).

As well as disease-related symptoms, patients experience treatment-related side effects such as fatigue, nausea, neuropathy, impaired cognitive functioning, and myelosuppression (9, 13). Tolerability profiles are a key factor for determining treatment choice in later lines of metastatic disease (7, 11, 47), and certain side effects may impact patients' ability to receive further therapy. For patients who have received two or more previous therapies for mCRC, current treatment options are associated with toxicities such as myelosuppression, fatigue and hand-foot syndrome (9, 10).

B.1.3.3.2 Humanistic burden

Whether disease- or treatment-related, the multiple symptoms of mCRC severely impact patients' health-related quality of life (HRQoL) (13). Patients with CRC also exhibit significantly high levels of psychological distress, with up to 57% and 47% of patients suffering from depression and anxiety, respectively (48). Depression and anxiety not only impair the quality of life (QoL) of patients with mCRC during treatment but are also associated with increased mortality risk (48).

The QoL of family and caregivers of patients with CRC are also negatively impacted. Fatigue and related symptoms affect the functioning of patients with CRC, which is associated with greater caregiver burden, and a negative impact on carers' mental and physical health, and QoL (49).

[2] An example of a typical continuum of care treatment sequence would include 4–6 months of 'induction' therapy, followed by 4–6 (–8) months of 'maintenance' therapy, then about 3 months re-introduction (or treatment beyond progression). The following therapy would be 5–7 months, followed by a treatment break before initiation of 3 months of a further therapy. This could potentially be followed by another therapy (in patients with RAS wild-type disease), then a few months of re-challenge of initial therapy, and finally a few months BSC only.

B.1.3.3.3 Economic burden

The cost of CRC in the UK was estimated at over £1.7 billion for the year 2018 (16, 17, 50). Direct expenditure on CRC care has been estimated at £307.8 million a year, which represents 18% of the total cost of CRC. The indirect economic impact, which measures the costs of premature death, temporary and permanent absence from work and unpaid informal care, was £1.4 billion a year, representing 82% of the total cost (50). In the UK, patients with CRC lose an average of 43 working days a year due to sick leave, and losses of earnings have been estimated at £129[3] a day per patient (51).

B.1.3.4 Clinical pathway of care

Around 85% of mCRC cases are unresectable and cannot be cured (11), and therefore the main aims of treatment for unresectable cases are to prolong survival while maintaining the best possible QoL (15) by minimising disease- and treatment-related symptoms. Most patients will receive treatment for the remainder of their lives, and when treatment options have been exhausted, are not tolerated or are contraindicated, patients will move to best supportive care (BSC) to manage symptoms and complications of their disease.

B.1.3.4.1 NICE guidelines

The National Institute for Health and Care Excellence (NICE) has issued the following documents with recommendations for the treatment of patients with mCRC:

- National guidelines (primary and secondary care): NG151 (last updated in December 2021) (52)
- The following technology appraisals were issued since the last NG151 update:
    - Regorafenib, TA866 (published February 2023) (53)
    - Pembrolizumab, TA914 (published September 2023) (54).

In the National Health Service (NHS) in England, treatment decisions for mCRC are based on genetic testing (biomarker-driven) and treatment in later lines is informed by prior therapy, the toxicity profile of the available medicines, and any previous treatment-related toxicities experienced by patients (11, 47). Figure 2 (Section B.1.3.4.4) shows the available

[3] Converted from Euros (EUR) to Great British Pounds (GBP) using the following online currency converter: https://www.xe.com/currencyconverter/convert/?Amount=148&From=EUR&To=GBP where 1 EUR = 0.871833 GBP (2nd November 2023)

treatments for patients with mCRC and aligns with feedback received from clinical experts at two advisory boards (one with 10 UK-based oncologists, held on 22nd September 2023, and one with four UK-based oncologists and three health economics advisors, held on 1st December 2023). The majority of patients with mCRC have unresectable disease, and will therefore begin first-line systemic treatment. First and second lines of systemic treatment include fluoropyrimidine-based (such as capecitabine and fluorouracil) chemotherapy combination regimens, typically FOLFOX (folinic acid, fluorouracil and oxaliplatin) or XELOX (capecitabine and oxaliplatin), FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin and irinotecan) or FOLFIRI (folinic acid, fluorouracil and irinotecan). Clinical experts have advised that most patients will receive fluoropyrimidine-based chemotherapy (± targeted treatments) in the first two lines of treatment, except for a small proportion (3–5%) who will receive immunotherapy/checkpoint inhibitors (11). Following second-line treatment, it is estimated 20-25% of patients will reach the third-line setting (53).

Pembrolizumab is available in the first-line setting and as a second-line option after fluoropyrimidine-based combination therapy, for patients with microsatellite instability-high [MSI-H] or MMR-deficient tumours. In the second and third-line settings, other biologics for patients with specific mutations include nivolumab + ipilimumab (patients with MSI-H or MMR-deficient tumours only) and encorafenib + cetuximab (patients with *BRAF* V600E mutations only). Nivolumab + ipilimumab is only recommended by NICE in patients with tumours positive for high microsatellite instability or MMR deficiency (19); encorafenib + cetuximab is only available to patients with a *BRAF* V600E mutation (20). Both nivolumab + ipilimumab and encorafenib + cetuximab are used following genetic testing of the tumour and earlier in the treatment pathway than the proposed positioning of fruquintinib, and are therefore not applicable to the population in this appraisal.

Takeda are seeking a recommendation for fruquintinib in [redacted]. For these patients, the following treatments are currently recommended by NICE:

- Regorafenib (VEGFR inhibitor): adult patients who have had previous treatment (including fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy) or when these treatments are unsuitable (NICE TA866 (7)). Unlike fruquintinib, which is highly selective for VEGFR tyrosine kinases, regorafenib targets other protein kinases as well as VEGFR kinases, including those involved in

oncogenesis (KIT proto-oncogene, receptor tyrosine kinase [KIT], proto-oncogene tyrosine-protein kinase receptor Ret [RET]), and the tumour microenvironment (platelet-derived growth factor receptor-like protein [PDGFR], fibroblast growth factor receptor [FGFR])

- Trifluridine-tipiracil: adult patients who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-VEGF agents and anti-EGFR agents, or for whom these available therapies are not suitable (NICE TA405 (55)). Trifluridine-tipiracil, also referred to as TAS-102, is a chemotherapy drug combining a nucleoside analogue (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil).

UK-based clinical experts have advised that, currently, patients generally receive trifluridine-tipiracil before regorafenib due to their familiarity with trifluridine-tipiracil and the challenging toxicity profile associated with regorafenib (11, 47). A minority of patients may receive regorafenib before trifluridine-tipiracil if they have progressed quickly on earlier fluorouracil-based chemotherapy, or are immunosuppressed. The positioning of fruquintinib alongside these comparators is further described in Section B.1.3.4.4.

B.1.3.4.2 Other clinical guidelines

The European Society for Medical Oncology (ESMO, (56)), the American Society of Clinical Oncology (ASCO, (57)) and the National Comprehensive Cancer Network (NCCN (12, 58)) all have guidelines for the treatment of mCRC. These are generally consistent with the NICE clinical guidelines, except for the following:

- ESMO, ASCO, and NCCN guidelines all recommend the use of the VEGF inhibitor bevacizumab in combination with other chemotherapy agents, as a first-line and/or subsequent therapy (8, 12, 57, 58). Bevacizumab, in combination with fluoropyrimidine-based chemotherapy, is licensed for use in the UK for the treatment of mCRC (59) but is not currently reimbursed (60). Anti-VEGF agents such as bevacizumab inhibit angiogenesis through neutralisation of VEGF and are different from anti-VEGFR agents such as fruquintinib and regorafenib, which inhibit VEGFR kinase activity

- NCCN guidelines recommend regorafenib or fruquintinib in patients previously treated with oxaliplatin and irinotecan (12, 58).

B.1.3.4.3 Unmet need

Patients with mCRC following prior treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, an anti-VEGF therapy, and an anti-EGFR therapy are deemed to have refractory disease (61) and have a poor prognosis, and face substantial disease- and treatment-related symptom burden.

Despite advances in the treatment of mCRC, many newer therapies in the first- and second-line settings only benefit select populations harbouring specific mutational drivers. For patients who have failed two previous lines of therapy, the only remaining active treatment options are trifluridine-tipiracil and regorafenib. However, trifluridine-tipiracil and regorafenib are associated with median PFS of 1.9–3.3 months, with disease control rates (DCR) of only 41–44%, and are associated with toxicities (9-11, 62). Clinical experts at the UK oncologist advisory board (22nd September 2023) commented that high rates of myelosuppression have been observed with trifluridine-tipiracil, with approximately 20% of patients requiring granulocyte colony-stimulating factor (G-CSF) to treat myelosuppression, and approximately 50% of patients having their treatment with trifluridine-tipiracil delayed due to unfavourable blood test results (9, 11). Toxicities such as fatigue and hand-foot syndrome are the primary reason for treatment discontinuation with regorafenib (10, 11). Therefore, there is a

substantial unmet need for an alternative treatment choice which provides a tolerable and manageable safety profile, and which does not negatively impact patient QoL.

For patients who have failed all existing treatment options, the only remaining option is BSC. Additionally, a proportion of patients will be contraindicated, or unable to tolerate active treatment and its related toxicities, and currently receive BSC on failure of two previous lines of therapy. Consequently, there is a high unmet medical need for alternative options that are well-tolerated, effective and which do not adversely impact QoL for patients who have been previously treated with or are not considered candidates for available therapies.

It is worth noting that the global randomised controlled trial (RCT) investigating fruquintinib (Section B.2.6), known as FRESCO-2, was conducted during the COVID-19 pandemic, when institutional participation in clinical studies was limited. Nevertheless, enrolment was completed in less than 17 months, which reinforces further the high unmet need for new treatment options in this population of patients with mCRC (63).

In relation, fruquintinib has been granted an innovation passport as part of the Innovative Licensing and Access Pathway (ILAP/IP/23/16189/02), based on it addressing a high unmet medical need and having the potential to offer benefits to patients by providing an effective and well-tolerated oral treatment option for patients with previously treated mCRC, including those who may be more susceptible to treatment-limiting adverse reactions associated with currently available therapies.

B.1.3.4.4 Proposed positioning of fruquintinib

The treatment pathway (including the proposed positioning of fruquintinib) for the treatment of patients with mCRC is presented in Figure 2. Takeda are seeking a recommendation for fruquintinib for the treatment of [redacted].

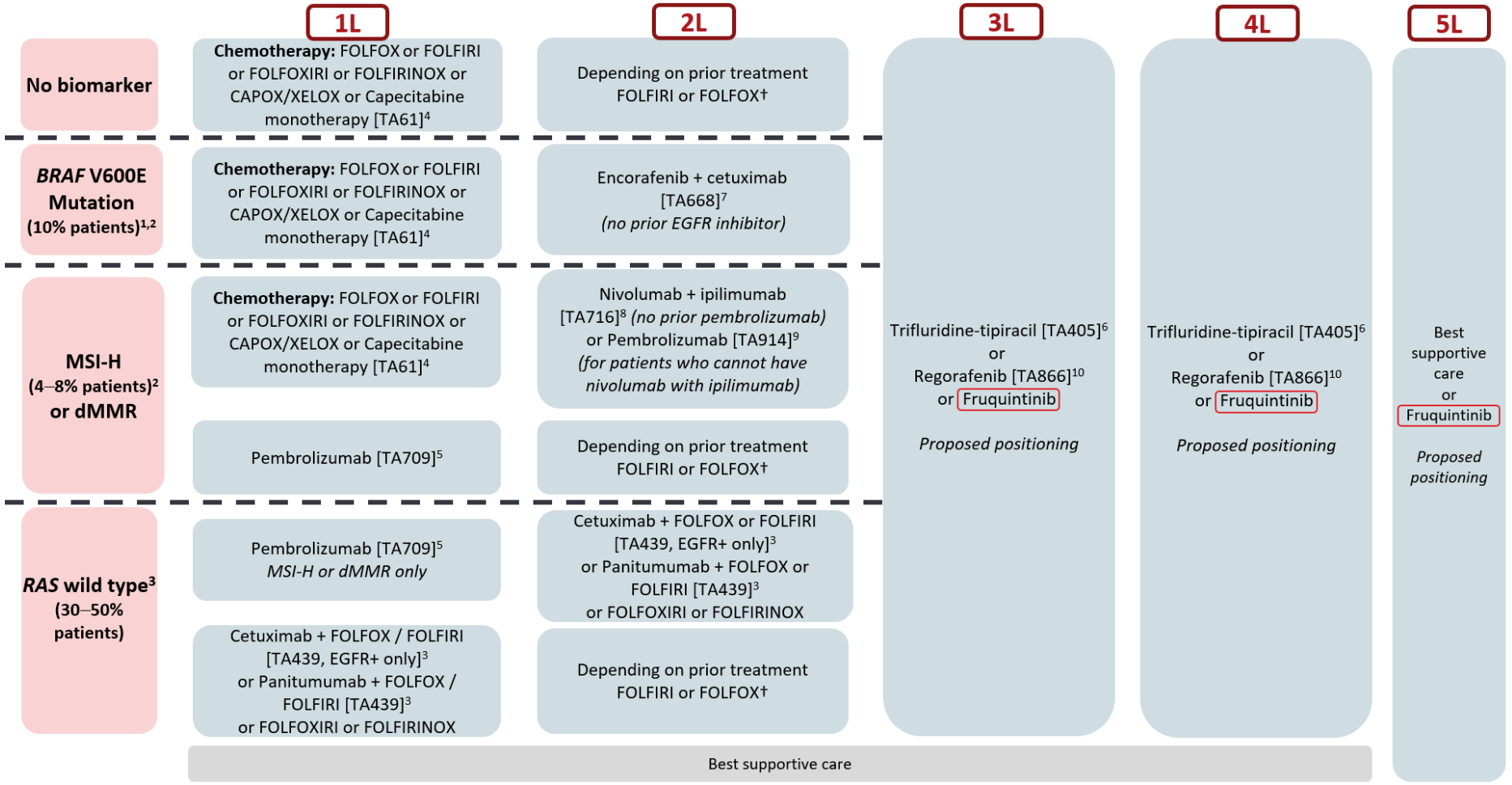
Fruquintinib is therefore expected to be used in the same position in the treatment pathway as trifluridine-tipiracil and regorafenib, in alignment with the populations recommended by NICE for these treatments. Feedback from clinical experts at the UK market access advisory board (1st December 2023) (47) stated that trifluridine-tipiracil monotherapy is expected to be replaced in the near future by trifluridine-tipiracil in combination with bevacizumab (subject to positive NICE guidance from the ongoing appraisal ID6298, currently under assessment by

the same Committee as fruquintinib [NICE Appraisal Committee B]), so the majority of fruquintinib use in UK clinical practice is expected to replace regorafenib use. Therefore, the most relevant comparator for decision making is deemed to be regorafenib.

Fruquintinib is also expected to be used in patients who have been previously treated with trifluridine-tipiracil and/or regorafenib, and in patients who are not considered candidates for any available therapies (i.e. where patients are currently receiving BSC). Therefore, BSC is also considered a relevant comparator in this population.

Clinicians at the UK oncologist advisory board (22nd September 2023) and UK market access advisory board (1st December 2023) agreed with the proposed positioning of fruquintinib and stated that it is in line with their expected use of it within the treatment pathway for mCRC (11, 47).

Figure 2: Proposed positioning of fruquintinib in the clinical pathway of care for mCRC



Sources: Grothey et al, 2021 (64), Van Cutsem et al, 2016 (8), NICE TA709 (65), NICE TA439 (66), NICE TA716 (67), NICE TA668 (68), NICE TA61 (69), TA405 (44), NICE TA866 (53), NICE TA914 (54).
†Trifluridine-tipiracil may be given if 1L FOLFOXIRI or FOLFIRINOX and other 2L treatments are not suitable.
Abbreviations: 1L, first line; 2L, second line; 3L, third line; 4L, fourth line; 5L, fifth line; BRAF, v-raf murine sarcoma viral oncogene homologue B; CAPOX/XELOX, capecitabine and oxaliplatin; dMMR deficient mismatch repair; EGFR, epidermal growth factor receptor, MSI-H, microsatellite instability-high; FOLFIRINOX, fluorouracil, irinotecan and oxaliplatin; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; mCRC, metastatic colorectal cancer; NICE, National Institute for Health and Care Excellence; RAS, rat sarcoma virus; TA, technology assessment.

B.1.4 Equality considerations

No equality issues relating to the use of fruquintinib have been identified.

B.2 Clinical effectiveness

The efficacy and safety of fruquintinib as a treatment for previously treated metastatic colorectal cancer (mCRC) was robustly assessed in two large Phase III randomised controlled trials (RCT), FRESCO and FRESCO-2

- In both trials, the efficacy and safety of fruquintinib plus best supportive care (BSC) was evaluated vs placebo plus BSC (henceforth referred to as placebo) in patients with refractory mCRC. In FRESCO (N=416), all patients had received chemotherapy, with a minority having had EGFR and/or VEGF inhibitors, whereas in FRESCO-2 (N=691), patients were more heavily pre-treated and had received chemotherapy, epidermal growth factor receptor (EGFR) and/or VEGF inhibitors, and trifluridine-tipiracil and/or regorafenib

In patients with previously treated mCRC, fruquintinib demonstrated statistically significant and clinically meaningful overall survival (OS) and progression-free survival (PFS) benefits, compared with placebo, while maintaining health-related quality of life (HRQoL)

- The FRESCO and FRESCO-2 trials provide a mature dataset
    - In FRESCO, median follow-up times were 13.3 months and 13.2 months for the fruquintinib and placebo arms, respectively, while in FRESCO-2, the median follow-up times were 11.3 months and 11.2 months for the fruquintinib and placebo arms, respectively
    - In FRESCO, 67.6% and 79.0% of patients experienced an OS event in the fruquintinib arm and placebo arms, respectively. In FRESCO-2, 68.8% and 75.2% of patients experienced an OS event in the fruquintinib arm in the placebo arms, respectively
    - In FRESCO, 84.5% and 90.6% of patients experienced a PFS event in the fruquintinib and placebo arms, respectively. In FRESCO-2, 85.0% and 92.6% of patients experienced a PFS event in the fruquintinib and placebo arms, respectively
- Both studies met their primary endpoint, OS, with consistent and statistically significant improvements observed with fruquintinib vs placebo
    - In FRESCO, median OS was 2.7 months longer with fruquintinib than placebo (9.3 vs 6.6 months), with a hazard ratio (HR) of 0.65 (95% confidence interval [CI]: 0.51, 0.83; p<0.001), indicating a 35% reduction in the risk of death with fruquintinib vs placebo
    - In FRESCO-2, median OS was 2.6 months longer with fruquintinib than placebo (7.4 vs 4.8 months), with an HR of 0.66 (95% CI: 0.55, 0.80; p<0.001), indicating a 34% reduction in the risk of death with fruquintinib vs placebo
- Both studies met their key secondary endpoint, PFS, with consistent and statistically significant improvements observed with fruquintinib vs placebo

    - In FRESCO, median PFS was 1.9 months longer with fruquintinib than placebo (3.7 vs 1.8 months) with an HR of 0.26 (95% CI: 0.21, 0.34; p<0.001), indicating a 74% reduction in the risk of disease progression or death with fruquintinib vs placebo
    - In FRESCO-2, median PFS was also 1.9 months longer with fruquintinib than placebo (3.7 vs 1.8 months), with an HR of 0.32 (95% CI: 0.27, 0.39; p<0.001), indicating a 68% reduction in the risk of disease progression or death with fruquintinib vs placebo
- Fruquintinib yielded a significant improvement in disease control rate (DCR) vs placebo in both trials (FRESCO: 62.2% vs 12.3%, p<0.001; FRESCO-2: 55.5% vs 16.1%; p<0.001)
- HRQoL of patients was evaluated in FRESCO-2 using Core Quality of Life (QLQ-C30) and EuroQol five-dimension five-level (EQ-5D-5L) questionnaires. Overall, HRQoL was not negatively impacted by treatment with fruquintinib, and patients in the fruquintinib arm had a slower worsening in clinical condition vs patients in the placebo arm
- Individual patient level data for FRESCO and FRESCO-2 were pooled to inform the majority of clinical inputs in the economic model, to reflect a population more representative of the UK landscape vs using either RCT independently, and to provide a greater sample size to inform analyses. Results from the pooled data analyses were consistent with those seen in FRESCO and FRESCO-2 independently, with statistically significant improvements observed with fruquintinib vs placebo for both OS (HR: 0.66; 95% CI: 0.57, 0.76; p<0.0001) and PFS (HR: 0.31; 95% CI: 0.27, 0.36; p<0.0001).

Network meta-analyses (NMA) were conducted to estimate relative efficacy (PFS and OS) for fruquintinib vs regorafenib, trifluridine-tipiracil, and placebo (BSC)

- Eight RCTs identified by the clinical SLR were included in the NMA
- NMA results showed that fruquintinib was associated with a significant advantage in both OS and PFS vs BSC, a significant advantage in PFS vs regorafenib and trifluridine-tipiracil, and a numerical advantage in OS vs regorafenib and trifluridine-tipiracil
    - PFS: fruquintinib was associated with a significant reduction in the hazard of progression or death vs BSC (HR: 0.30 [95% credible interval [CrI]: 0.26, 0.34]), and was associated with a significant reduction in the hazard of progression or death vs both trifluridine-tipiracil and regorafenib (HR: 0.67 [95% CrI: 0.55, 0.80] and HR: 0.66 [95% CrI: 0.54, 0.81], respectively). The cumulative probability of fruquintinib being ranked first in the network ahead of trifluridine-tipiracil and regorafenib was 100%
    - OS: fruquintinib was associated with a significant reduction in the risk of death vs BSC (HR: 0.66 [95% CrI: 0.57, 0.76]), and was associated with a numerical advantage vs trifluridine-tipiracil (HR: 0.95 [95% CrI: 0.78, 1.15]) and vs regorafenib (HR: 0.93 [95% CrI: 0.75, 1.16]). The cumulative probability of fruquintinib ranking first in the network over trifluridine-tipiracil and regorafenib was 81%

- A series of scenario analyses were conducted to explore the impact of imbalance in the distribution of potential treatment effect modifiers between studies on the NMA results. Results remained broadly consistent with the base case, suggesting minimal influence on the overall conclusions

Fruquintinib was generally well tolerated, with associated treatment-emergent adverse events (TEAEs) being manageable, and generally reversible; most TEAEs resolved with dose modification and/or drug discontinuation

- In FRESCO, median treatment exposure was 3.7 months (range: 0.1–21.9 months) for fruquintinib and 1.8 months (range: 0.1–11.1 months) for placebo, with a mean relative dose intensity (RDI) of 92.0% in the fruquintinib arm and 98.0% in the placebo arm
    - The most common TEAEs of any grade experienced by patients treated with fruquintinib were hypertension (55.4%), hand-foot syndrome (49.3%), and proteinuria (42.1%)
    - Grade ≥3 TEAEs occurred in 61.2% of patients receiving fruquintinib vs 19.7% receiving placebo
    - Most TEAEs occurred during the first two cycles of treatment and could be managed with supportive care and dose adjustment
- In FRESCO-2, median treatment exposure was 3.1 months (range: 0.3–19.1) for fruquintinib and 1.8 months (range: 0.3–12.0) for placebo, with a mean RDI of 85.0% in the fruquintinib arm and 89.3% in the placebo arm
    - The most common TEAEs of any grade experienced by patients treated with fruquintinib were hypertension (36.8%), asthenia (34.0%), and decreased appetite (27.2%)
    - Grade ≥3 TEAEs occurred in 62.7% of patients receiving fruquintinib vs 50.4% receiving placebo
    - Most TEAEs, including hypertension, asthenia, and hand-foot syndrome, could be managed with supportive care and dose modification

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted on 4th October 2023 to identify all relevant clinical evidence on the efficacy, safety, and treatment-related health-related quality of life (HRQoL) in 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-vascular endothelial growth factor (VEGF) therapy, and, if RAS wild type, an anti-epidermal growth factor receptor (EGFR) therapy. See Appendix D for full details of the process and methods used to identify the clinical evidence relevant to fruquintinib.

In total, the SLR identified 382 records reporting on 281 unique studies (see Appendix D, Figure 1). Of the 281 unique studies, most were observational in nature (216 studies; 77%),

followed by single-arm trials (41 studies, 15%), and RCTs (23 studies, 8%). Across the included studies, 124 evaluated trifluridine-tipiracil (± bevacizumab), 130 regorafenib, 40 rechallenge treatment, and 17 fruquintinib. See Appendix D (Section D.2.1, Figure 1) for the study selection process and Appendix D (Section D.2.5) for the full list of included studies.

Of the total included studies, 17 evaluated fruquintinib: three were RCTs (FRESCO, FRESCO-2 and NCT02196688; reported across 15 publications); two were single-arm trials (NCT03251378 and NCT01975077; reported across four publications); and, 12 were observational studies of fruquintinib (reported across 13 publications (70-82). A summary of identified fruquintinib evidence and the linked primary and secondary publications is provided in Table 4. Detailed descriptions of study characteristics, patient characteristics, treatment characteristics and outcomes for included RCTs, single-arm studies and observational studies evaluating fruquintinib is provided in Appendix D (Section D.2.2, Section D.2.3 and Section D.2.4, respectively).

Table 4. Identified clinical effectiveness evidence of fruquintinib in the clinical SLR

Study Name (Registration)	Primary publication	Secondary publication
Randomised controlled trials of fruquintinib		
FRESCO (NCT02314819)	Li, 2018 (83)	Li, 2020 (84); Qin, 2021 (85); Takeda, 2017 (86) (CSR);Xu, 2021 (87)
FRESCO-2 (NCT04322539)	Dasari, 2023a (63)	Dasari, 2022 (88); Dasari, 2023b (89); Eng, 2023 (90); Hutchison Medipharma Limited, 2023 (91); Sobrero, 2023 (92); Takeda, 2023 (93) (CSR); Yoshino, 2022 (94)
NCT02196688†	Xu 2017a (95)	Hutchison Medipharma Limited, 2020 (96)
Single arm trials of fruquintinib		
NCT03251378	Dasari, 2020 (97)	Dasari, 2022 (98); Dasari, 2020b (99)
NCT01975077†	Xu, 2017(95)†	–
Observational studies of fruquintinib		
NCT04005066	Li, 2023b (79)	–
Cui, 2020	Cui, 2020 (70)	–
Dai, 2022	Dai, 2022 (71)	Qiu, 2021 (75)
Deng, 2023	Deng, 2023 (72)	–
He, 2023	He, 2023 (81)	–
Jin, 2022	Jin, 2022 (73)	–
Li, 2023a	Li, 2023a (79)	–

Study Name (Registration)	Primary publication	Secondary publication
Liu, 2022	Liu, 2022 (74)	–
Song, 2021	Song, 2021 (76)	–
Wang, 2020	Wang, 2020 (78)	–
Wang, 2022	Wang, 2022 (80)	–
Zhang, 2022	Zhang, 2022 (77)	–
Zhang, 2023	Zhang, 2023 (82)	–

†Note this publication (Xu, 2017 (95)) reported data from Phase 1b (NCT01975077; single-arm trial) and Phase 2 [NCT02196688; RCT] and this study appears in both the study listing for RCTs and single-arm trials. Therefore, the count of study publications by study design does not sum to match the total publications.
Abbreviations: CSR, clinical study report; RCT, randomised controlled trial; SLR, systematic literature review.

In addition, of the 20 included RCTs evaluating regorafenib and trifluridine-tipiracil, two unique RCTs (reported across six publications (10, 100-104)) evaluating regorafenib, and three RCTs (reported in seven publications (9, 105-110)) evaluating trifluridine-tipiracil in patients with mCRC were synthesised in a network meta-analysis (NMA) with the three fruquintinib RCTs (Section B.2.8). Eight RCTs in total were therefore included in the NMA. See Section B.2.1 and Appendix D (Section D.3.1, Figure 6) for the study selection process for the NMA. Detailed descriptions of study characteristics, patient characteristics, treatment characteristics, efficacy outcomes, subgroup data, and safety outcomes from the RCTs evaluating regorafenib and trifluridine-tipiracil is provided in Appendix D (Section D.2.2.1, Section D.2.2.2, Section D.2.2.3, Section D.2.2.4, Section D.2.2.5, and Section D.2.2.6, respectively).

B.2.2 List of relevant clinical effectiveness evidence

Three RCTs evaluating fruquintinib were identified by the clinical evidence SLR: one Phase II RCT (NCT02196688 (95)) and two pivotal Phase III RCTs (FRESCO [NCT02314819] (83, 86) and FRESCO-2 [NCT04322539] (63, 93)).

Data from the pivotal Phase III RCTs, FRESCO (NCT02314819 (83, 86)) and FRESCO-2 (NCT04322539 (63, 93)), form the main evidence base for this submission (Table 5). These RCTs were prioritised due to their Phase III design. A pooled analysis of the FRESCO and FRESCO-2 trials was conducted; these data are presented in Section B.2.6.3 and were used to inform clinical parameters in the cost-effectiveness model.

The Phase II RCT (95, 96) was a randomised, double-blind, placebo-controlled, multicentre trial to compare the efficacy and safety of fruquintinib + best supportive care (BSC) vs placebo + BSC in patients with mCRC who have progressed after second-line or above standard chemotherapy. The Phase II RCT was included in the NMA to estimate the relative

effect of fruquintinib compared with regorafenib and trifluridine-tipiracil to ensure all available evidence was used to inform the comparisons.

A summary of the identified single-arm and observational studies of fruquintinib is provided in Appendix D. Data from these studies is used to compare and support the RCT data from FRESCO and FRESCO-2.

Table 5: Clinical effectiveness evidence for fruquintinib

Study	FRESCO (NCT02314819)	FRESCO-2 (NCT04322539)
Study design	Randomised, double-blind, placebo-controlled, multicentre, Phase III study	Randomised, double-blind, placebo-controlled, multicentre, Phase III study
Population	Adult patients with mCRC who have failed two prior lines of treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, ± VEGF or EGFR inhibitors	Adult patients with refractory mCRC who have progressed on or been intolerant to treatment with chemotherapy, biological therapy and trifluridine-tipiracil and/or regorafenib
Intervention	Fruquintinib 5 mg PO, QD + BSC, 3 weeks on, 1 week off	Fruquintinib 5 mg PO, QD + BSC, 3 weeks on, 1 week off
Comparator	Placebo + BSC	Placebo + BSC
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes. In the economic model, clinical inputs for fruquintinib and BSC were informed by pooled data from FRESCO and FRESCO-2, including baseline characteristics, PFS, OS and TTD for fruquintinib and PFS and OS for BSC, AE rates, RDI and subsequent therapies	
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	• OS • PFS • Response rates, including BOR, DCR and ORR • DOR • Adverse effects of treatments	• OS • PFS • Response rates, including BOR, DCR and ORR • DOR • Adverse effects of treatments • HRQoL
All other reported outcomes	N/A	N/A
Sources of evidence	Published data sources • Li et al, 2018 (primary manuscript) (83) • Secondary data sources (84-87) Unpublished data source: • CSR (86)	Published data sources • Dasari et al, 2023 (primary manuscript) (63) • Secondary data sources (88-94) Unpublished data source: • CSR (93)

Abbreviations: AE, adverse event; BOR, best overall response; BSC, best supportive care; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; mCRC, metastatic colorectal cancer; N/A, not applicable; ORR, objective response rate; OS, overall survival;

PFS, progression-free survival; PO, orally; QD, once daily; QLQ-C30, Core Quality of Life questionnaire; RDI, relative dose intensity; TTD, time to treatment discontinuation; VEGF, vascular endothelial growth factor.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study design

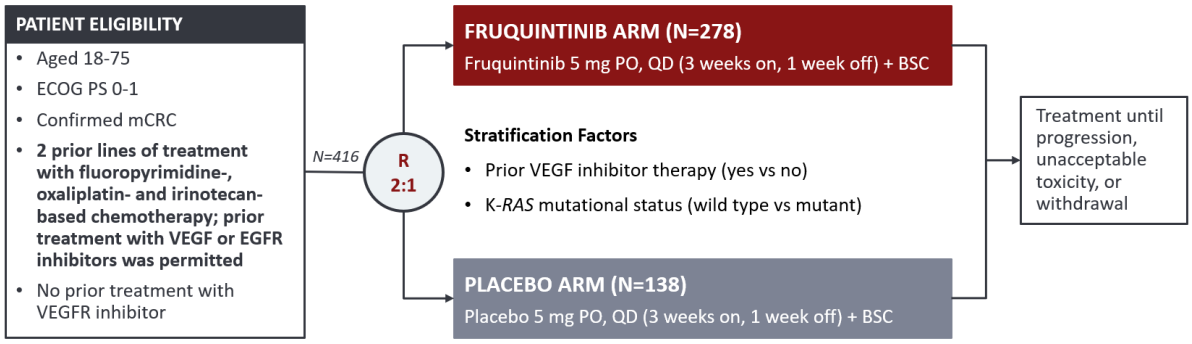
B.2.3.1.1 FRESCO

FRESCO was a randomised, double-blind, placebo-controlled, multicentre, Phase III trial that evaluated the efficacy and safety of fruquintinib + BSC (henceforth referred to as the fruquintinib arm) vs placebo + BSC (the placebo arm) in adults with mCRC who had tumour progression following treatment regimens that included fluoropyrimidine, oxaliplatin, and irinotecan. The study was conducted across 28 centres in China.

Patient eligibility included histological or cytological documentation of mCRC, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and failure of at least second-line standard chemotherapy. Treatment failure was defined as occurrence of progressive disease (PD) or intolerance to toxic side-effects during treatment or within 3 months after the last treatment. Patients who had previously been treated with a VEGFR inhibitor were ineligible for the trial (Table 6).

After patients were deemed to meet the screening eligibility criteria, they were randomised 2:1 to the fruquintinib arm or placebo arm. In the fruquintinib arm, patients received fruquintinib 5 mg once a day (QD), via oral administration, three weeks on, one week off combined with BSC. BSC was defined within the FRESCO and FRESCO-2 trial protocol as any treatment necessary for health and not anticipated to interfere with study drug and was determined locally by the investigator. BSC therefore excluded other anti-tumour agents, radiotherapy (except palliative radiation), biotherapy, endocrine therapy, or any other study drug treatment. In the placebo arm, patients received a fruquintinib placebo 5 mg QD, via oral administration, 3 weeks on, 1 week off combined with BSC (Figure 3). Stratified randomisation was performed, and the stratification factors were prior use of VEGF inhibitors (yes vs no) and *K-Ras* gene status (wild type vs mutant type).

Figure 3: FRESCO study design



Abbreviations: BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor; K-RAS, Kirsten rat sarcoma viral oncogene homologue; mCRC, metastatic colorectal cancer; PO, orally; QD, once daily; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Each treatment cycle consisted of 28 days. Throughout the study and within 30 days after end of treatment, safety and tolerability was evaluated. All patients received the study drug until they experienced PD according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, death, intolerable toxicity, withdrawal of consent, the attending physician deems the termination of treatment to be in the patients' best interests or other criteria for termination of treatment were met. A computed tomography/magnetic resonance imaging (CT/MRI) examination was performed every eight weeks.

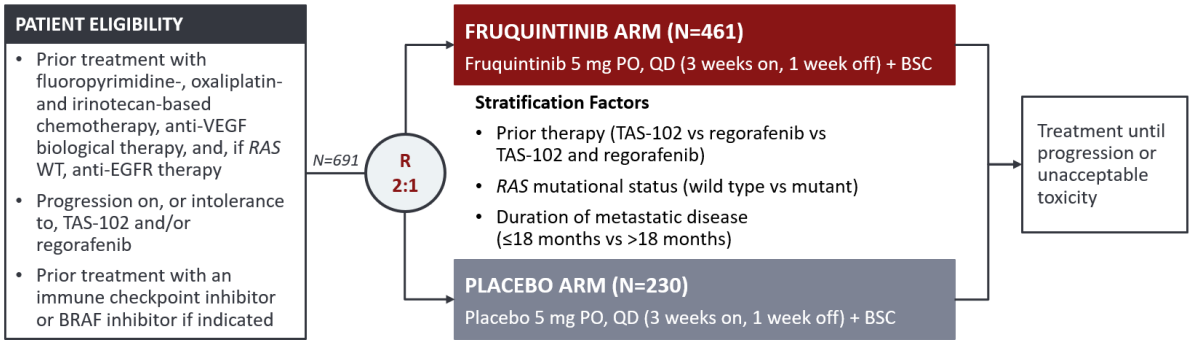
B.2.3.1.2 FRESCO-2

FRESCO-2 was a randomised, double-blind, placebo-controlled, multicentre, Phase III study that compared the efficacy and safety of fruquintinib + BSC vs placebo + BSC in adults with mCRC who had progressed on or were intolerant to chemotherapy, biologics, and trifluridine-tipiracil and/or regorafenib. A total of 124 centres randomised patients to the study across Australia, Europe, Japan and the United States (US). There were three centres in the UK, which enrolled three patients overall. This low recruitment figure may be explained by the inclusion criteria which required that patients should have received an anti-VEGF therapy, which is currently not reimbursed in the UK (60); however, clinical experts at the advisory board conducted by Takeda in September 2023 stated that FRESCO-2 was nevertheless generalisable to the UK population, since the trial enrolled patients who were similar to the UK with regard to age, race and geographical location (11).

Patient eligibility included histological or cytological documentation of mCRC, ECOG PS of 0 or 1, previous treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF biological therapy, an anti-EGFR therapy (if *RAS* wild type) and progression on or intolerance to treatment with trifluridine-tipiracil and/or regorafenib (Table 6).

After patients were deemed to meet the screening eligibility criteria, they were randomised 2:1 to the fruquintinib arm or placebo arm. In the fruquintinib arm, patients received fruquintinib 5 mg once a day (QD), via oral administration, three weeks on, one week off combined with BSC. BSC was defined within the FRESCO and FRESCO-2 trial protocol as any treatment necessary for health and not anticipated to interfere with study drug and was determined locally by the investigator. BSC therefore excluded other anti-tumour agents, radiotherapy (except palliative radiation), biotherapy, endocrine therapy, or any other study drug treatment. In the placebo arm, patients received a fruquintinib placebo 5 mg QD, via oral administration, 3 weeks on, 1 week off combined with BSC (Figure 4). Stratified randomisation was performed, and the stratification factors were prior therapy (trifluridine-tipiracil vs regorafenib vs trifluridine-tipiracil and regorafenib), *RAS* gene status (wild type vs mutant type) and duration of metastatic disease (≤18 months vs >18 months).

Figure 4: FRESCO-2 study design



Abbreviations: BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor; K-RAS, Kirsten rat sarcoma viral oncogene homologue; mCRC, metastatic colorectal cancer; PO, orally; QD, once daily; TAS-102, trifluridine-tipiracil; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Each treatment cycle consisted of 28 days. Patients' safety assessment and drug accountability were performed at each treatment cycle. All patients received the study drug until the patients experienced PD according to RECIST v1.1, death, intolerable toxicity, withdrawal of consent, the attending physician deems the termination of treatment to be in the patients' best interests or other criteria for termination of treatment were met.

B.2.3.2 Trial methodology

An overview of the trial methodology for FRESCO and FRESCO-2 is presented in Table 6. A summary of all inclusion and exclusion criteria is presented in Appendix M.

Table 6: Summary of trial methodology – FRESCO and FRESCO-2

	FRESCO	FRESCO-2
Trial design	Randomised, double-blind, placebo-controlled, multicentre, Phase III study	
Trial aim	To evaluate the efficacy and safety of treatment with fruquintinib versus placebo in patients with advanced CRC who have failed second-line or later standard chemotherapy	To compare the efficacy and safety of fruquintinib versus placebo in patients with refractory mCRC
Trial location	China, 28 centres	Global: 124 centres across Australia (6), Europe (91), Japan (10) and the US (45)
Study phases	• Screening/baseline: from Day –21 to Day 1 (before the first administration of the investigational drug) • Treatment phase: Day 1 of Cycle 1 to EOT (including 1 week of discontinuation) • Follow-up phase: EOT phase to end of trial	• Screening period: from Day –28 to Day 1 (before the first administration of the investigational drug) • Study treatment period: Day 1 of Cycle 1 to Cycle 4 and beyond • Follow-up: EOT (1 week after discontinuation of study drug), safety follow-up (30 days after EOT visit) and survival follow-up (every 12 weeks from EOT visit)
Trial drug – intervention	Fruquintinib 5 mg PO QD for 3 weeks of continuous dosing followed by a 1-week break (3 weeks on/1 week off), plus BSC. Each treatment cycle consisted of 28 days	
Trial drug – comparator	Placebo 5 mg PO QD for 3 weeks of continuous dosing followed by a 1-week break (3 weeks on/1 week off) plus BSC. Each treatment cycle consisted of 28 days	
Key inclusion criteria	• Histologically and/or cytologically diagnosed mCRC (Stage IV) • Had previously received and failed at least second-line standard chemotherapy. The standard treatment regimens must have included fluorouracil, oxaliplatin and irinotecan. Treatment failure is defined as: occurrence of PD or intolerance to toxic side-effects during treatment or within 3 months after the last treatment • Each line of treatment for PD included ≥1 chemotherapy drug with a duration of drug administration of ≥1 cycle • Prior adjuvant/neoadjuvant therapy was allowed. If recurrence or metastases occurred during adjuvant/neoadjuvant therapy or within 6 months after completion, it was considered a failure of	• Histologically and/or cytologically documented mCRC. *RAS*, *BRAF*, and MSI/MMR status was documented according to country-level guidelines • Progressed on or were intolerant to treatment with trifluridine-tipiracil and/or regorafenib. Patients were considered intolerant to trifluridine-tipiracil or regorafenib if they received at least 1 dose of either agent and were discontinued from therapy for reasons other than PD. Patients who had been treated with both trifluridine-tipiracil and regorafenib were eligible. Patients were previously treated with the following: ○ Standard approved therapies: fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy ○ An anti-VEGF biological therapy ○ If *RAS* wild type, an anti-EGFR therapy ○ If MSI-H or dMMR, immune checkpoint inhibitors if approved and available in the patient's country unless the

	FRESCO	FRESCO-2
	adjuvant/neoadjuvant therapy as first-line systemic chemotherapy targeted to PD • Prior anti-tumour treatment regimens that used chemotherapy combined with targeted drugs such as cetuximab, panitumumab or other EGFR inhibitors or VEGF inhibitors were allowed • Had not undergone systematic chemotherapy or radiation therapy, immunotherapy, biological or hormone therapy and other anti-tumour therapies in the past 4 weeks; had never received treatment with VEGFR inhibitors • Aged 18–75 years • Weight ≥40 kg • ECOG PS ≤1 • LVEF ≥50% • Measurable lesions that met the requirements of RECIST v1.1 were clearly defined • Expected survival >12 weeks	patient was ineligible for treatment with a checkpoint inhibitor ○ If *BRAF*-mutant, a BRAF inhibitor if approved and available in the patient's country unless the patient was ineligible for treatment with a BRAF inhibitor • Aged ≥18 years (Japan: ≥20 years) • Weight ≥40 kg • ECOG PS ≤1 • Measurable lesions according to of RECIST v1.1, locally assessed • Expected survival >12 weeks
Key exclusion criteria	• Hypertension that cannot be controlled with monotherapy, i.e. systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg after monotherapy • Had not recovered from toxic reactions from previous anti-cancer treatments (NCI CTCAE Grade 1, but did not include hair loss and ≤ grade 2 neurotoxicity caused by oxaliplatin), had not fully recovered from previous surgery or it had been less than 4 weeks since the previous anti-cancer therapy or surgery • CNS metastases or prior brain metastases • History of arterial thrombus or DVT within 6 months before enrolment, or patients with evidence of bleeding tendency	• Uncontrolled hypertension, i.e. systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg despite optimal medical management. Patients were required to have blood pressure values below both limits. Repeated assessments were permitted • History of a thromboembolic event, including DVT, PE, or arterial embolism within6 months prior to screening • Stroke or TIA within 12 months prior to screening • Clinically significant CVD, including but not limited to acute MI, or coronary artery bypass within 6 months before enrolment, severe or

	FRESCO	FRESCO-2
	within two months before enrolment, regardless of the severity • Stroke or TIAs within 12 months prior to enrolment • Had acute MI, serious/unstable angina pectoris or underwent coronary artery bypass within 6 months before enrolment; or Class 2 and above NYHA cardiac insufficiency	unstable angina pectoris; NYHA CHF, ventricular arrythmias requiring treatment, or LVEF <50% • Any unresolved toxicities from a previous antitumour treatment greater than NCI CTCAE v 5.0 Grade 1 (except for alopecia or neurotoxicity Grade ≤ 2) • Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy, and without clinical imaging evidence of stable disease for 14 days or longer; patients requiring steroids within 4 weeks prior to start of study treatment were excluded
Prior and concomitant therapies	**Permitted** • Based on the principal investigator's judgment, all drugs that were necessary for the health of patients and were not expected to interfere with the evaluation of the study. This included anticoagulants and LMW heparin sodium if required for treatment **Prohibited** • Anti-tumour therapies, including cytotoxic drugs (except for non-anti-tumour chemotherapy), radiotherapy (except for palliative radiation therapy for symptom control), biotherapy, endocrine therapy or any other study drug treatment at the time of enrolment and during the entire study. Systemic anti-tumour therapies or other study drug treatments had to be completed at least 4 weeks before enrolment into FRESCO • Traditional Chinese medicine with anti-tumour indications	**Permitted** • Oral contraceptives, hormone-replacement therapy, or other allowed maintenance therapy could be continued if indicated • Prophylactic use of anti-coagulation for the maintenance of patency of permanent indwelling central venous access devices or for patients at high risk of venous thromboembolism • Prophylactic antiemetic, granulocyte colony stimulating factors, granulocyte macrophage colony-stimulating factors, platelet simulating factors or erythropoietin, as clinically indicated • Palliative radiation for symptom control was allowed, provided it did not compromise tumour assessments of target lesions. However, study treatment had to be suspended during the radiation period and not resumed until at least 7 days after radiation, and only if radiation-related toxicities had resolved to Grade ≤ 2 and no PD was observed • All supportive measures consistent with optimal patient care **Prohibited** • Any therapy intended for the treatment of cancer, whether currently marketed or experimental, including, but not limited to, the following: chemotherapy, hormonal therapy, biologic therapy, radiotherapy (except palliative radiation as described above), or herbal therapy • Concomitant use of medications that have a known risk of causing QT prolongation and/or torsades de pointes • Live vaccines were prohibited during the study and for 3 months after the last dose of study drug

	FRESCO	FRESCO-2
Efficacy assessment	• Tumour assessment was performed according to the RECIST v1.1. The tumour imaging assessment method was determined by the investigator to be CT or MRI. If tumour assessment had been performed within 21 days prior to the first drug administration and the same method was used at the same hospital, it could be used as baseline tumour assessment. Baseline tumour assessment had to include the chest, abdomen, pelvis and any other sites suspected to have tumour lesions, and the slice thickness had to be 5 mm • Target lesion record: number of lesions, site, description, largest diameter measurement of each lesion (except lymph nodes) and smallest diameter measurement of lymph nodes, including the sum of diameter of all target lesions • The tumour status was evaluated using imaging once every 8 weeks after patients received treatment until PD. In order to evaluate tumours accurately, the CT or MRI for all patients, in addition to being assessed by the site investigator, was passed to a third party for independent interpretation, without affecting the investigator's judgment	• The antitumour efficacy determination was based on tumour response using RECIST v1.1, including PFS, and ORR. Tumour evaluation was performed by image-based evaluation (contrast-enhanced CT or MRI imaging scan) every 8 weeks until PD, death, new anticancer treatment, study treatment discontinuation, or study completion, whichever occurred first. For all patients, the RECIST v1.1 tumour response data were used to determine each patient's visit response (TPR) based on investigator's assessment according to RECIST v1.1 and the BOR
Follow-up	Survival follow-up (telephone follow-up) was performed every 2 months from the EOT visit, and information on all subsequent antitumor treatments and trial-related SAEs was collected. For patients who did not have disease progression, if the tumour evaluation result could be obtained, the follow-up tumour evaluation results were recorded in the CRF until disease progression was confirmed. The date and cause of death was recorded, if applicable. Patients who withdrew informed consent also entered the follow-up period. If the patient clearly states that he/she refused to participate in follow-up when withdrawing informed consent, this patient terminated the trial and survival follow-up was not performed. Prior to the end of the entire trial, survival follow-up was uniformly performed on all patients who survived, and survival follow-up was not performed on patients again after the end of the entire trial	Survival follow-up (by telephone) was performed every 12 weeks (± 2 weeks) after the EOT visit. All subsequent antitumor therapy and information about study drug-related serious TEAEs were collected. For the patients who discontinued the study without PD, all available tumour assessment results during survival follow-up were recorded in the eCRF until confirmation of PD. The date and cause of death was recorded, if applicable. Patients who withdrew consent were encouraged to be followed for survival. If the patient had clearly expressed his or her refusal to be followed after withdrawal of consent, he or she terminated the study, and no follow-up for survival was performed

	FRESCO	FRESCO-2
Primary outcomes	OS, defined as the time interval between randomisation and the date of death caused by any reason. For patients who were not reported dead as of the analysis, the date of the last known survival was used as the censored date	OS, defined as the time (months) from date of randomisation to death from any cause Patients without report of death at the time of analysis were censored at the date last known alive Patients lacking data beyond the date of randomisation had their survival time censored at the date of randomisation

Other outcomes used in the economic model/specified in the scope	• PFS, defined as the time between randomisation to objective PD as per RECIST v1.1 or death (if there was no progression, death due to any reason)
	• BOR, defined as the best efficacy recorded from randomisation to objectively recorded progression as per RECIST v1.1 or the start of subsequent anti-cancer treatment (whichever occurs first)
	• ORR, defined, according to RECIST v1.1, as the percentage of patients with BOR of CR or PR as compared to baseline
	• DCR, defined as the percentage of patients with BOR of CR, PR or stable disease. If the BOR was stable disease, the time interval between randomisation and the confirmation of stable disease had to be at least 53 days
	• DOR, defined as the time from the patient's first objective CR or PR, (whichever occurs first) to the time of occurrence of PD or death
	• Safety endpoints including AEs, laboratory results, vital signs, weight, ECG and echocardiography and ECOG PS
		• PFS, defined as the time from randomisation until the first radiographic documentation of objective progression, as assessed by the investigator using RECIST v1.1, or death from any cause
		• ORR, calculated using 2 methods:
		  ○ Method 1: ORR was calculated using a strict interpretation of RECIST v 1.1
		  ○ Method 2: $ORR_{UNCONFIRMED}$ was calculated using all responses regardless of confirmation.
		• DCR, defined as the proportion of patients with a BOR of confirmed CR, confirmed PR, or stable disease for 7 weeks
		• DOR, defined as the time from the first occurrence of PR or CR by RECIST v1.1, until the first date that PD was documented by RECIST v1.1 or death, whichever came first
		• PROs endpoints, derived based on the EORTC QLQ-C30 (version 3.0) and EuroQol five-dimension five-level (EQ-5D-5L) questionnaires
		• Safety endpoints including AEs, serious TEAEs, and AESIs

	FRESCO	FRESCO-2
Pre-planned subgroups	• Subgroup analyses of OS and PFS • Demographic information: Age (<65, ≥65 years) and sex • Baseline cancer characteristics: primary tumour site, laterality, metastasis (single, multiple), presence of liver metastases, and ECOG PS • Time from 1st metastatic diagnosis to randomisation (<18, ≥18 months) • Prior systemic anti-cancer therapies: • Prior VEGF inhibitors • Prior EGFR inhibitors • Prior targeted treatment • Number of prior treatment lines (≤3, >3) • Number of prior treatment lines for metastatic disease (≤3, >3) • *KRAS* status	• Subgroup analyses of OS and PFS • Demographic information: Age (<65, ≥65 years), sex, race and region • Baseline cancer characteristics: primary tumour site, laterality, metastasis (single, multiple), metastasis site other than colon or rectum (single, multiple), presence of liver metastases, and ECOG PS • Time from 1st metastatic diagnosis to randomisation (<18, ≥18 months) • Prior systemic anti-cancer therapies: • Prior therapy with trifluridine-tipiracil and regorafenib • Prior VEGF inhibitors • Prior EGFR inhibitors • Prior treatment with immune checkpoint inhibitors for MSI-H/dMMR • Prior targeted treatment • Number of prior treatment lines (≤3, >3) • Number of prior treatment lines for metastatic disease (≤3, >3) • Biomarker status: *RAS, BRAF* and microsatellite/mismatch repair

Source: FRESCO final CSR (86), FRESCO-2 final CSR (93).
Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BOR, best overall response; BRAF, v-raf murine sarcoma viral oncogene homologue B; BSC, best supportive care; CHF, congestive heart failure; CNS, central nervous system; CR, complete response; CSR, clinical study report; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CVD, cardiovascular disease; DCR, disease control rate; DNA, deoxyribonucleic acid; dMMR, deficient mismatch repair; DVT, deep vein thrombosis; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer – Core Quality of Life questionnaire; EOT, end of treatment; EQ-5D-5L, EuroQol five-dimension five-level; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalised ratio; IP, investigational product; IV, intravenous; IVC, inferior vena cava; KRAS, Kirsten rat sarcoma viral oncogene homologue; LMW, low-molecular weight; LVEF, left ventricular ejection fraction; mCRC, metastatic colorectal cancer; MI, myocardial infarction; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NCI, National Cancer Institute; NYHA, New York Heart Association; ORR, objective response rate; OS, overall survival; PD, progressive disease; PE, pulmonary embolism; PFS, progression-free survival; PO, orally; PR, partial response; PRO, patient-reported outcomes; QD, once daily; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumours; SVC, superior vena cava; TEAE, treatment-emergent adverse event; TIA, transient ischaemic attack; TKI, tyrosine kinase inhibitor; TPR, time point response; ULN, upper limit of normal; US, United States; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

B.2.3.3 Demographics and baseline characteristics

Table 7 presents a summary of baseline demographics and disease characteristics for patients in FRESCO and FRESCO-2.

FRESCO: Baseline demographics between the two arms were generally well balanced. The mean age was 54.6 years (fruquintinib arm: 54.3 years, standard deviation [SD]:10.70; placebo arm: 55.1 years. SD: 10.53). In both arms, the majority of patients had an ECOG PS of 1 (fruquintinib: 72.3%, placebo: 73.2%). All patients recruited were from China. There were more male than female patients in both arms, but this was more notable in the placebo arm (29.7% of patients were female, 70.3% male) than the fruquintinib arm (43.2% female, 56.8% male) (Table 7).

Disease characteristics were also well balanced between the fruquintinib and placebo arms. The majority of patients in FRESCO had received two or three prior lines of therapy (fruquintinib arm: 68.3%; placebo arm: 71.0%). Less than a third of patients (fruquintinib arm: 30.2%; placebo arm: 29.7%) had previously received a VEGF inhibitor.

FRESCO-2: Similar to FRESCO, baseline demographics between the two arms were generally well balanced (Table 7). The mean age was 62.3 years (fruquintinib arm: 62.2 years, SD: 10.41; placebo arm: 62.4 years, SD: 9.67). In both arms, the majority of patients had an ECOG PS of 1 (fruquintinib: 57.5%, placebo: 55.7%). The majority of patients recruited were from Europe (fruquintinib arm: 71.4%, placebo arm: 72.2%). There were more male than female patients in both arms, but once again this was more notable in the placebo arm (39.1% of patients were female, 60.9% male) than in the fruquintinib arm (46.9% female, 53.1% male).

Disease characteristics were also well balanced between the fruquintinib and placebo arms. Patients in FRESCO-2 were more heavily pre-treated than in FRESCO, with the majority of patients having received more than three prior lines of therapy (fruquintinib arm: 83.3%; placebo arm: 80.9%). Unlike in FRESCO, the majority of patients (fruquintinib arm: 96.5%, placebo arm: 96.1%) had previously been treated with a VEGF inhibitor (mostly bevacizumab).

FRESCO and FRESCO-2 both enrolled patients who had received at least two prior lines of systemic therapy for mCRC; the majority of patients had Stage III or IV disease at first diagnosis and there were more male than female patients. Despite there being some differences between the trial populations (e.g. the Asian-only population in FRESCO, and the proportions of patients receiving prior anti-VEGF), advisors at the UK oncologist advisory

board (22nd September 2023) stated that the two trials offer strong data packages that complement each other well, and provide a compelling rationale for the use of fruquintinib across patient subgroups and treatment lines. Advisors agreed that both trials are highly relevant for clinical decision-making and together comprise an evidence base generalisable to the UK population (11): in particular, FRESCO is representative of the UK population's currently low rate of exposure to anti-VEGF treatments (e.g. bevacizumab which is not reimbursed in the UK), while FRESCO-2 enrolled patients that were more similar to the UK with regard to age, race and geographical location. Of note, patients in FRESCO-2 were more heavily pre-treated than in FRESCO, which is typically associated with a worse prognosis than for patients who have had fewer lines of therapy (7).

Table 7: Summary of baseline demographics and disease characteristics – FRESCO and FRESCO-2, ITT population

Category	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230
Age, years				
Mean (SD)	54.3 (10.70)	55.1 (10.53)	62.2 (10.41)	62.4 (9.67)
Sex, n (%)				
Female	120 (43.2)	41 (29.7)	216 (46.9)	90 (39.1)
Male	158 (56.8)	97 (70.3)	245 (53.1)	140 (60.9)
Race, n (%)				
American Indian or Alaska native	0	0	0	1 (0.4)
Asian	278 (100)	138 (100)	43 (9.3)	18 (7.8)
Black or African American	0	0	13 (2.8)	7 (3.0)
Native Hawaiian or other Pacific Islander	0	0	3 (0.7)	2 (0.9)
White	0	0	367 (79.6)	192 (83.5)
Other	0	0	5 (1.1)	2 (0.9)
Multiple races	0	0	2 (0.4)	0
Not reported/unknown	0	0	28 (6.1)	8 (3.5)
Ethnicity, n (%)				
Han Chinese	272 (97.8)	135 (97.8)	0	0
Non-Han Chinese	6 (2.2)	3 (2.2)	0	0
Hispanic or Latino	0	0	20 (4.3)	14 (6.1)
Not Hispanic or Latino	0	0	405 (87.9)	202 (87.8)
Not reported/unknown	0	0	36 (7.8)	14 (6.1)
Region and Country, n (%)				
China	278 (100)	138 (100)	0	0
North America	0	0	82 (17.8)	42 (18.3)

Category	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230
Europe	0	0	329 (71.4)	166 (72.2)
Asia Pacific (Japan and Australia)	0	0	50 (10.8)	22 (9.6)
BMI (kg/m^2)				
n	278	138	450	225
Mean (SD)	23.19 (3.286)	23.52 (3.429)	26.00 (5.159)	25.77 (5.218)
ECOG PS, n (%)				
0	77 (27.7)	37 (26.8)	196 (42.5)	102 (44.3)
1	201 (72.3)	101 (73.2)	265 (57.5)	128 (55.7)
Time since first diagnosis of CRC (months)				
n	277[†]	138	461	230
Mean (SD)	2.24 (1.548)	2.43 (1.788)	52.74 (30.406)	56.02 (28.846)
Median	1.79	2.04	47.18	49.38
Min, max	0.1, 9.7	0.3, 9.8	6.0, 242.4	7.1, 154.4
Stage of CRC at first diagnosis, n (%)				
Stage I	8 (2.9)	4 (2.9)	20 (4.3)	6 (2.6)
Stage II	34 (12.2)	18 (13.0)	32 (6.9)	17 (7.4)
Stage III	118 (42.4)	51 (37.0)	139 (30.2)	84 (36.5)
Stage IV	117 (42.1)	63 (45.7)	264 (57.3)	119 (51.7)
Missing	1 (0.4)	2 (1.4)	6 (1.3)	4 (1.7)
Primary site at first diagnosis, n (%)				
Colon	147 (52.9)	70 (50.7)	279 (60.5)	137 (59.6)
Rectum	125 (45.0)	60 (43.5)	143 (31.0)	70 (30.4)
Colon-rectum	6 (2.2)	7 (5.1)	39 (8.5)	23 (10.0)
Missing	0	1 (0.7)	0	0
Primary tumour location at first diagnosis, n (%)				
Left (splenic flexure, descending/transverse /sigmoid colon and rectum)	214 (77.0)	115 (83.3)	335 (72.7)	162 (70.4)
Right (caecum, ascending colon and hepatic flexure)	56 (20.1)	21 (15.2)	97 (21.0)	53 (23.0)
Left and right	4 (1.4)	0	4 (0.9)	2 (0.9)
Unknown	4 (1.4)	1 (0.7)	25 (5.4)	13 (5.7)
Missing	0	1 (0.7)	0	0
Duration of metastatic disease (months)				
n	278	138	461	230
Mean (SD)	18.92 (12.946)	20.57 (14.626)	44.01 (23.978)	46.65 (24.607)
Median	16.03	17.22	37.88	40.97
Min, max	0.9, 79.0	1.9, 81.6	6.0, 192.8	7.1, 147.1

Category	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230
Categories, n (%)				
<18 months‡/≤18 months§	163 (58.6)	75 (54.3)	37 (8.0)	13 (5.7)
≥18 months‡/>18 months§	115 (41.4)	63 (45.7)	424 (92.0)	217 (94.3)
Liver metastases, n (%)				
Yes	185 (66.5)	102 (73.9)	339 (73.5)	156 (67.8)
No	93 (33.5)	36 (26.1)	122 (26.5)	74 (32.2)
***KRAS*‡/*RAS*§ gene status, n (%)**				
Wild type	157 (56.5)	74 (53.6)	170 (36.9)	85 (37.0)
Mutant	121 (43.5)	64 (46.4)	291 (63.1)	145 (63.0)
***BRAF*§ gene status, n (%)**				
Wild type	NR	NR	401 (87.0)	198 (86.1)
V600E mutation	NR	NR	7 (1.5)	10 (4.3)
Other mutation	NR	NR	53 (11.5)	22 (9.6)
Microsatellite/Mismatch repair status, n (%)				
MSS and/or pMMR	NR	NR	427 (92.6)	215 (93.5)
MSI-H and/or dMMR	NR	NR	5 (1.1)	4 (1.7)
Unknown	NR	NR	29 (6.3)	11 (4.8)
Prior use of VEGF inhibitor, n (%)				
Yes	84 (30.2)	41 (29.7)	445 (96.5)	221 (96.1)
No	194 (69.8)	97 (70.3)	16 (3.5)	9 (3.9)
Prior use of EGFR inhibitor, n (%)				
Yes	40 (14.4)	19 (13.8)	180 (39.0)	88 (38.3)
No	238 (85.6)	119 (86.2)	281 (61.0)	142 (61.7)
Prior treatment with EGFR/VEGF inhibitors, n (%)				
No anti-VEGF and no anti-EGFR	167 (60.1)	83 (60.1)	4 (0.9)	5 (2.2)
Anti-VEGF, anti-EGFR or both	111 (39.9)	55 (39.9)	457 (99.1)	225 (97.8)
Anti-VEGF and no anti-EGFR	71 (25.5)	36 (26.1)	277 (60.1)	137 (59.6)
Anti-EGFR and no anti-VEGF	27 (9.7)	14 (10.1)	12 (2.6)	4 (1.7)
Both anti-VEGF and anti-EGFR	13 (4.7)	5 (3.6)	168 (36.4)	84 (36.5)
Prior treatment with trifluridine-tipiracil and/or regorafenib, n (%)§				
Trifluridine-tipiracil	0	0	240 (52.1)	121 (52.6)
Regorafenib	0	0	40 (8.7)	18 (7.8)
Trifluridine-tipiracil and regorafenib	0	0	181 (39.3)	91 (39.6)
Number of prior treatment lines				
Median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)

Category	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230
2 or 3, n (%)	190 (68.3)	98 (71.0)	77 (16.7)	44 (19.1)
>3, n (%)	88 (31.7)	40 (29.0)	384 (83.3)	186 (80.9)
Number of prior treatment lines for metastatic disease, n (%)				
≤3	221 (79.5)	107 (77.5)	125 (27.1)	64 (27.8)
>3	57 (20.5)	31 (22.5)	336 (72.9)	166 (72.2)

Source: FRESCO final CSR (84), FRESCO tables (111), FRESCO-2 final CSR (19), Dasari et al, 2023 (20).
†Time of first diagnosis was missing for one patient; ‡FRESCO only; §FRESCO-2 only.
Abbreviations: BMI, body mass index; BRAF, v-raf murine sarcoma viral oncogene homologue B; BSC, best supportive care; CSR, clinical study report; CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor; ITT, intention-to-treat; KRAS, Kirsten rat sarcoma viral oncogene homologue; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NR, not reported; pMMR, proficient mismatch repair; Q, quartile; RAS, rat sarcoma virus; SD, standard deviation; VEGF, vascular endothelial growth factor.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis sets

In both FRESCO and FRESCO-2, efficacy analyses were conducted on the intention-to-treat (ITT) set, which included all randomised patients. Safety analyses were conducted on the safety set, which included all patients who had received at least one dose of the study treatment drug. Sensitivity analyses on OS were conducted on the per protocol (PP) set, which included patients without major protocol deviations that could affect survival analysis. FRESCO-2 also included a pharmacokinetics (PK) set, which was used to collect concentration data for fruquintinib and metabolite M11 (Table 8).

Table 8: Analysis sets – FRESCO and FRESCO-2

Analysis set	FRESCO	FRESCO-2
Full patient set/ Screened population	Includes all patients who provided informed consent for the study	
ITT set	Includes all randomised patients. Patients were analysed by treatment group as randomised. The ITT population was the primary population for evaluating all efficacy endpoints and patient characteristics according to the treatment they were assigned	
Safety analysis set	Includes all patients in the ITT set who received at least one dose of study drug. Patients in this population were analysed according to the treatment they actually received. This set was used for all safety analyses/endpoints	
PP population	Includes patients in the ITT set without major protocol deviations that could affect OS analysis. OS analysis was performed based on this population to assess the stability of the primary analysis results based on ITT	Includes patients in the ITT set who received the treatment to which they were randomised to and had no major protocol deviations that precluded the assessment of efficacy and/or data integrity. Patients who took the wrong treatment at any time during the study were excluded from the PP population. The PP population was used for sensitivity analyses of OS and PFS and could be used to analyse selected endpoints to test the robustness of results. The criteria for inclusion in the PP subset were finalised and documented prior to study unblinding
PK population	N/A	Includes all patients who received at least one dose of study drug and had at least one post-dose PK sample collected and analysed. The PK population was used for tabulation of fruquintinib and M11 concentrations from PK plasma samples

Source: FRESCO final CSR (86), FRESCO-2 final CSR (93).
Abbreviations: ITT, intention-to-treat; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PP, per protocol.

B.2.4.2 Statistical analysis

Table 9 presents a summary of the statistical analyses performed in FRESCO and FRESCO-2, and a summary of censoring methods for secondary endpoints is presented in Appendix M. In both studies, subgroup analyses were performed on OS and PFS to test the consistency of OS and PFS treatment effects in different subsets. Multiple sensitivity analyses were performed on OS and PFS to evaluate the impact of different analysis components on efficacy outcomes.

Table 9: Summary of statistical analysis – FRESCO and FRESCO-2

Analysis	FRESCO	FRESCO-2
Hypothesis objective	To compare the efficacy and safety of fruquintinib plus BSC vs placebo plus BSC in patients with advanced CRC who have failed the second-line and above standard chemotherapy. In this study, a superiority test was performed to compare fruquintinib with placebo.	To demonstrate superiority of fruquintinib plus BSC (fruquintinib arm) over placebo plus BSC (placebo arm) in prolonging OS for patients with refractory mCRC. The study was designed to test the null hypothesis H0: λ=1.0 versus the alternative hypothesis Ha: λ<1.0, where λ is the hazard ratio (treatment arm/placebo arm)
Statistical analysis	**Main analyses** OS was compared between treatment groups with a stratified log-rank test performed based on the actual prior use of VEGF inhibitors and *KRAS* gene status. Based on the KM method, the median survival time, quartile survival time, the 3-, 6-, 9-, 12- and 18-month survival of each treatment arm and the corresponding 95% CI were estimated. The HR and the corresponding 95% CI were estimated based on stratified Cox proportional hazards model. PFS was compared between treatment groups with a stratified log-rank test. HR was estimated through the stratified Cox proportional hazards model, and the corresponding 95% CI was calculated. Of which, the stratification factors were the same as that in the OS analysis. The median and quartile PFS of the various treatment arms at 1, 3 and 6 months, PFS and their 95% CI were obtained through KM and the corresponding KM curve was plotted. **Other secondary endpoints:** In each treatment arm, the exact 95% CI of ORR or DCR estimate was estimated using the Clopper-Pearson method. The stratified CMH test method was used to calculate odds ratio and its CI and p-value based on the stratification factors. Stratified exact test was performed if the number of ORR or DCR patients was	**Main analyses** For OS and PFS, between-treatment comparisons were performed. Multiplicity-adjusted p-values were reported and were the basis for the anti-tumour efficacy conclusions and claim at the 2-sided significance level of 0.0499. KM plots were produced, and the median, 25% and 75% percentiles of time to event were estimated using the KM method with their corresponding 95% CIs. The two-sided p-values to test the treatment effect were calculated using a stratified log-rank test accounting for randomisation schedule stratification factors. The HRs between the two treatment groups, together with the 95% CIs, were calculated from a stratified Cox proportional hazards model in which the treatment group was the only covariate in the model. For OS, a summary of the duration of follow-up was also provided. Multiplicity-adjusted p-values were reported. The adjusted p-value for OS was its raw p-value. A fixed-sequence (hierarchical) testing procedure was used to control the overall type I error rate at 0.05. If the resulting 2-sided p-value from the analysis of primary endpoint OS was ≤ 0.05, then a superiority test for PFS was conducted at the 2-sided significance level of 0.05.

	insufficient to support CMH test and the odds ratio and the exact CI were presented For patients who had no response after randomisation, descriptive analysis was performed for DOR For each treatment arm, the results were shown through the KM estimates and distribution curve. The analysis of the duration of stable disease was also carried out using similar methods. **Subgroup analyses – OS and PFS** For each subgroup, the patients and frequency of events, and median OS/PFS estimated by KM were listed and the treatment grouping was used as the only covariate to obtain HR and its corresponding 95% CI through the unstratified Cox proportional hazard model, and the forest plot was used to display the subgroup analysis results. **Sensitivity analyses** The following sensitivity analyses were performed on OS in the ITT population: The unstratified log-rank test was used to compare the two treatment arms, to evaluate the impact of non-stratification on the results The stratified log-rank test and stratified Cox proportional hazards model were used to repeat the analysis in the ITT population, and the difference was that the stratified data used in the analysis was from the IWRS As an exploratory study, the stratified multi-factor Cox proportional hazard model was fitted to assess the effect of relevant baseline demographic characteristics on the estimation of HR, and the stratification information came from the actual stratification data recorded by the CRF To further assess the robustness of the primary analysis results of OS, analysis of OS was repeated based on the PP set The sensitivity analysis of the PFS in the 2 treatment arms was compared based on the unstratified log-rank test to evaluate the stratification effect. HR and its corresponding 95% CI were estimated through the unstratified Cox proportional hazards model. In addition, sensitivity analysis was performed on PFS endpoints based on the ITT analysis set using a different censoring rule from the primary analysis	Multiplicity-adjusted p-values were reported, the adjusted p-value for PFS is the maximum value between the p-values produced for the OS and PFS. Other secondary efficacy endpoints included ORR, DCR, and DOR. According to the RECIST v1.1, TPR (CR, PR, stable disease, PD, or NE) for each patient was collected, then the BOR for the patient (confirmed CR, confirmed PR, stable disease, PD, or NE) was obtained based on the TPR. The ORR (confirmed CR and confirmed PR) and DCR (confirmed CR, confirmed PR, and stable disease for 7 weeks) were obtained based on the BOR. Patients in each TPR category were presented in a data listing. The number and percentage of patients in each category of BOR, ORR, ORR unconfirmed, and DCR were summarised. Estimates of response rate, along with its associated exact 2-sided 95% CIs, were computed using the Clopper-Pearson method for ORR and DCR within each treatment group. The binary endpoint of ORR for the two treatment groups was analysed using a stratum-adjusted method to account for the stratification factors. The adjusted proportion difference and its 95% CIs were calculated using the Wald method. The 2-sided p-value was calculated using a stratified CMH method. The median and 25th and 75th percentiles of DOR, estimated using the Kaplan-Meier method along with their 95% CIs generated from the method by Brookmeyer and Crowley were reported **Subgroup analyses – OS and PFS** Subgroup analyses were conducted based on the unstratified Cox proportional hazard model in which the applicable randomisation schedule stratification factors and treatment group are included in the model as covariates. Forest plots were used to display the subgroup analyses results. **Sensitivity analyses** Sensitivity analyses were performed, including the OS and PFS analyses based on the PP population. The p-value was obtained from the stratified log-rank test, and the HRs between the two treatment groups together with 95% CIs, were calculated. Forest plots were used to display the subgroup analyses results.

Sample size and power calculation	The estimated number of primary endpoint events needed was based on the following hypothesis: • Two-tailed significance level of 0.05 • Detection of an HR of 0.7 in OS of the study to control group with a power of 80% is equivalent to prolongation of the median OS from 6.3 months to 9 months. The enrolment rate was 30 patients per month, which was to be reached within 3 months after the start of study. Based on these assumptions, approximately 400 patients were to be enrolled in approximately 15 months in the study. The PFS was analysed and summarised when approximately 300 PFS events were observed after one month post the end of enrolment. The OS was analysed and summarised when 280 OS events were observed after 7 months after the end of enrolment. At the same time, the sample size was adjusted accordingly based on the result of the phase II fruquintinib study in colorectal cancer (95) and the newest available data of overall survival from the study with placebo in the third line and above therapy for advanced CRC.	The total sample size and number of OS events required for efficacy assessment in the ITT population were calculated based on the following assumptions: • A 1-sided significance level of 0.025. • Assuming an OS HR of 0.73 (fruquintinib group/placebo group), this sample size yields approximately 90% statistical power to detect superiority of the fruquintinib group over the placebo group. If the true median OS for the placebo group was 5 months, then the HR of 0.73 corresponds to median OS of 6.8 months in the fruquintinib group (median OS improvement of 1.8 months). • Enrolment rate of 30 patients per month during the first 3 months and 50 patients per month thereafter • Yearly dropout rate of 10%. • Randomisation ratio = 2:1 (fruquintinib group/placebo group). • Data maturity = 70%. One interim futility analysis when one-third of the total number of OS events (i.e. 160 OS events) had occurred; the Lan-DeMets spending function was used in the calculation
Data management and patient withdrawals	For OS, duration to follow-up referred to the time interval between randomisation date and last date known to be alive for patients who had not yet been reported to have died by the time of analysis. Patients who were reported to have died would be censored at death date	For OS (calculated as [date of death or last known alive – date of randomisation + 1]/30.4375), patients without report of death at the time of analysis were censored at the date last known alive. Patients lacking data beyond the date of randomisation had their survival time censored at the date of randomisation. OS was not censored if a patient received subsequent anticancer treatments after discontinuation of the study treatments

Source: FRESCO protocol (112), FRESCO SAP (113), FRESCO-2 SAP (114).
Abbreviations: BOR, best overall response; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CR, complete response; CRC, colorectal cancer; CRF, case report form; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; ITT, intention-to-treat; IWRS, Interactive Web Response Systems; KM, Kaplan-Meier; KRAS, Kirsten rat sarcoma viral oncogene homologue; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PP, per protocol; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SAP, statistical analysis plan; TPR, time point response; VEGF, vascular endothelial growth factor.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of FRESCO and FRESCO-2 was conducted using the Cochrane RoB v2, the full details of which are provided in Appendix D. Both RCTs were reported to have low concerns in respect of bias. Overall, both studies were considered to be methodologically robust, high-quality studies with an overall low risk of bias. Of note, there are observed differences in ethnicity and the proportion of patients with exposure to anti-VEGF therapy between FRESCO and FRESCO-2.

In terms of ethnicity, FRESCO was conducted in an Asian-only population, whereas FRESCO-2 was a global study with 8.8% of patients who were Asian. Clinical expert opinion elicited at the UK market access advisory board (1st December 2023) stated that ethnicity is not a treatment effect modifier in this population. Similar clinical opinion was reported in TA866. This is also supported by the FRESCO-2 subgroup data for PFS, which demonstrated comparable HRs for fruquintinib vs BSC for the Asian subgroup vs the ITT population (HR 0.29 [95% confidence interval [CI]: 0.14, 0.58] vs HR 0.32 [95% CI: 0.27, 0.39], respectively) (Section B.2.7).

In FRESCO-2, 96.5% of patients had received a prior anti-VEGF therapy (predominantly bevacizumab) vs 30% of patients in FRESCO. FRESCO was considered more representative of UK practice given that anti-VEGF treatments (e.g. bevacizumab) are not reimbursed for use in mCRC in the UK. Clinical expert opinion elicited at the UK market access advisory board (1st December 2023) stated that prior anti-VEGF therapy is likely a treatment effect modifier. However, subgroup data for OS from FRESCO estimated HRs of 0.68 (95% CI: 0.45, 1.03) and 0.60 (95% CI: 0.45, 0.80) which were numerically, but not statistically, different for fruquintinib vs BSC for patients who have vs haven't received prior anti-VEGF (Section B.2.7).

Advisors at the UK oncologist advisory board (22nd September 2023) stated that the two trials offer strong data packages that complement each other well, and that both trials together comprise an evidence base generalisable to the UK population (Section B.2.6.3).

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 Patient disposition

Appendix D contains the participant flow for FRESCO and FRESCO-2.

FRESCO: A total of 519 patients were screened, of which 416 were randomised to either fruquintinib or placebo (ITT set; Table 10). In the ITT set, 415 patients initiated treatment; one patient in the placebo arm was not administered the study treatment and was therefore excluded from the safety analysis set. A total of 404 patients were included in the PP set (Table 10). At the end of the treatment period, 24 patients (8.6%) were still receiving treatment in the fruquintinib arm vs 1 patient (0.7%) in the placebo arm. In the fruquintinib arm, 254 patients (91.4%) had discontinued treatment, vs 136 patients (98.5%) in the placebo arm: 197 patients (70.9%) had disease progression (vs 111 patients [80.4%] on placebo), 33 patients (11.9%) had intolerable toxicity (vs 6 patients [4.3%] on placebo), 15 patients (5.4%) were withdrawn from the study by the Investigator (vs 4 patients [2.9%] on placebo), 5 patients (1.8%) withdrew consent (vs 13 patients [9.4%] on placebo), and 4 patients (1.4%) died (vs 2 patients [1.4%] on placebo) (Appendix D).

FRESCO-2: A total of 934 patients were screened, of which 691 were randomised to either fruquintinib or placebo (ITT set; Table 10). In the ITT set, 686 patients initiated treatment; five patients in the fruquintinib arm did not receive the study drug, of whom two were administered placebo. A total of 669 patients were included in the PP set. A total of 331 patients had at least one post-dose PK sample collected and were included in the PK analysis set (Table 10). At the end of the treatment period, 20 patients (4.3%) were still receiving treatment in the fruquintinib arm vs 1 patient (0.4%) in the placebo arm. In the fruquintinib arm, 438 patients (95.0%) had discontinued treatment, vs 227 patients (98.7%) in the placebo arm: 271 patients (58.8%) had disease progression (vs 147 patients [63.9%] on placebo), 91 patients (19.7%) due to AEs (vs 40 patients [17.4%] on placebo), 31 patients (6.7%) were withdrawn from the study by the Investigator (vs 18 patients [7.8%] on placebo), 16 patients (3.5%) decided to leave the study but agreed to future follow-up (vs 3 patients [1.3%] on placebo), 6 patients (1.3%) withdrew consent and did not agree to future follow-up (vs 2 patients [0.9%] on placebo), 4 patients (0.9%) died (vs 4 patients [1.7%] on placebo), 1 patient (0.2%) was lost to follow-up (vs 0 in the placebo arm) and 18 patients (3.9%) discontinued treatment for other reasons (vs 13 patients [5.7%] on placebo) (Appendix D).

Table 10: Patient disposition within analysis sets – FRESCO and FRESCO-2

Analysis set	FRESCO			FRESCO-2		
	Fruquintinib + BSC n (%)	Placebo + BSC n (%)	All patients n (%)	Fruquintinib + BSC n (%)	Placebo + BSC n (%)	All patients n (%)
Screened population	–	–	519	–	–	934
ITT set	278 (100)	138 (100)	416 (100)	461 (100)	230 (100)	691 (100)
Safety set	278 (100)	137 (99.3)	415 (99.8)	456 (98.9)	230 (100)	686 (99.3)
PP population	275 (98.9)	130 (94.2)	405 (97.4)	444 (96.3)	225 (97.8)	669 (96.8)
PK population	N/A			329 (71.4)	2 (0.1)	331 (47.9)

Source: FRESCO final CSR (86), FRESCO-2 final CSR (93).
Abbreviations: BSC, best supportive care; CSR, clinical study report; ITT, intention-to-treat; N/A, not applicable; PK, pharmacokinetics; PP, per protocol.

B.2.6.2 Clinical effectiveness

The efficacy data presented in this submission are mature and taken from the final data cuts of the FRESCO and FRESCO-2 RCTs. Median follow-up times in FRESCO were 13.3 months and 13.2 months for the fruquintinib and placebo arms, respectively, and in FRESCO-2, 11.3 months and 11.2 months for the fruquintinib and placebo arms, respectively. In both trials, OS and PFS data were mature: in FRESCO, 67.6% patients in the fruquintinib arm and 79.0% in the placebo arm experienced an OS event, and 84.5% of patients in the fruquintinib arm and 90.6% in the placebo arm experienced a PFS event. In FRESCO-2, 68.8% of patients in the fruquintinib arm and 75.2% in the placebo arm had experienced an OS event, with 85.0% of patients in the fruquintinib arm and 92.6% in the placebo arm experiencing a PFS event.

In addition, advisors at the UK oncologist advisory board (22nd September 2023) stated that both trials are highly relevant for clinical decision-making and together comprise an evidence base generalisable to the UK population (7): FRESCO is representative of the UK population's currently low rate of exposure to anti-VEGF treatments (e.g. bevacizumab which is not reimbursed in the UK), while FRESCO-2 enrolled patients that were demographically more similar to the UK with regard to age, race and geographical location. Overall, results are very consistent between the two trials and support the increased efficacy of fruquintinib vs placebo in previously treated mCRC.

B.2.6.2.1 Primary endpoint: OS

Both FRESCO and FRESCO-2 met their primary endpoints of OS, with statistically significant improvements in OS observed with fruquintinib vs placebo. The improvement in OS is considered clinically meaningful, particularly in this later-line setting where prognosis is extremely poor.

FRESCO: As of the final data cut-off (DCO) date (17th January 2017), the median duration of treatment was 3.7 months in the fruquintinib arm and 1.8 months in the placebo arm. Median follow-up time was 13.3 months in the fruquintinib arm and 13.2 months in the placebo arm. A total of 188 patients (67.6%) in the fruquintinib arm and a total of 109 patients (79.0%) in the placebo arm had died. At the end of the study, 83 patients (29.9%) in the fruquintinib arm and 24 patients (17.4%) in the placebo arm were still alive.

Median OS was 9.3 months with fruquintinib compared with 6.6 months with placebo (i.e. an OS benefit of 2.7 months with fruquintinib), with a hazard ratio (HR) of 0.65 (95% CI: 0.51, 0.83; p<0.001), indicating that the risk of death in the fruquintinib arm reduced by 35% compared with placebo (Table 11). The Kaplan-Meier (KM) curves showed an early separation in favour of fruquintinib, which was maintained over the duration of the study (Figure 5).

FRESCO-2: As of the final DCO (24th June 2022), the median duration of treatment was 3.1 months in the fruquintinib arm and 1.8 months in the placebo arm. Median follow-up time was 11.3 months in the fruquintinib arm and 11.2 months in the placebo arm. At the end of the study, 127 patients (27.5%) in the fruquintinib arm and 49 patients (21.3%) in the placebo arm were still alive.

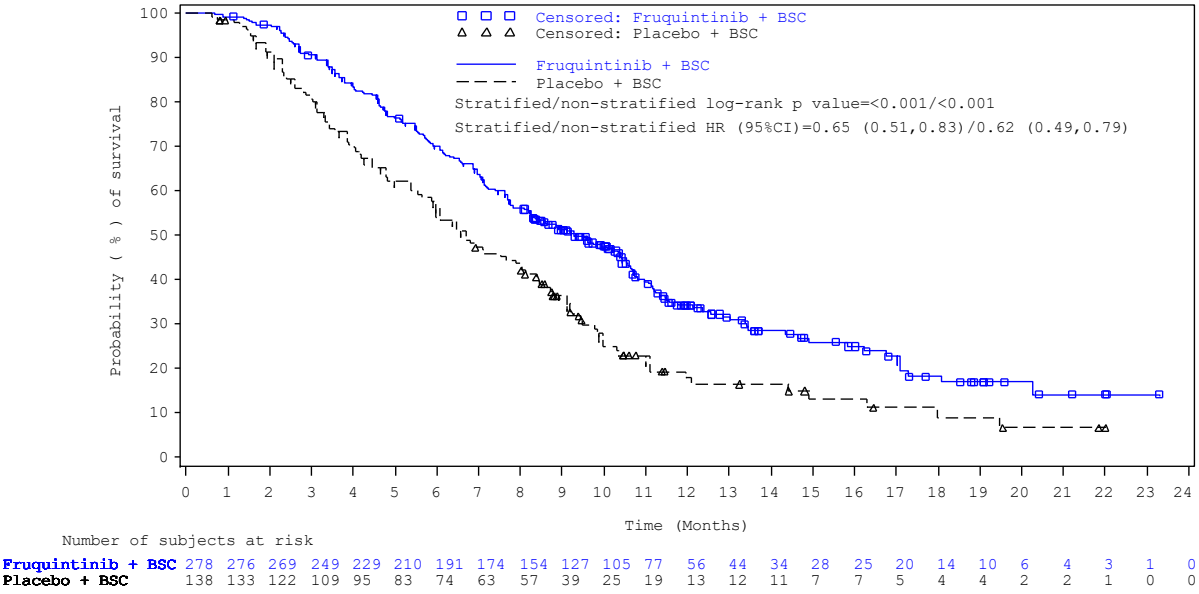
Median OS was 7.4 months with fruquintinib compared with 4.8 months with placebo (i.e. 2.6 months longer with fruquintinib), with an HR of 0.66 (95% CI: 0.55, 0.80; p<0.001), indicating that the risk of death in the fruquintinib arm was reduced by 34% compared with placebo (Table 11). Similar to those observed in FRESCO, the KM curves showed an early separation in favour of fruquintinib (Figure 6).

Table 11: Summary of OS – FRESCO and FRESCO-2, ITT population

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=138**	**Fruquintinib + BSC N=461**	**Placebo + BSC N=230**
No. of patients who died, n (%)	188 (67.6)	109 (79.0)	317 (68.8)	173 (75.2)
No. of patients censored, n (%)	90 (32.4)	29 (21.0)	144 (31.2)	57 (24.8)
Censoring reasons, n (%)				
Alive	83 (29.9)	24 (17.4)	127 (27.5)	49 (21.3)
Lost to follow-up	3 (1.1)	1 (0.7)	3 (0.7)	0
Withdrawal of consent	4 (1.4)	4 (2.9)	14 (3.0)	8 (3.5)
OS (months)				
Median (95%CI)	9.30 (8.18, 10.45)	6.57 (5.88, 8.11)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
Probability (%) of being alive at: (95% CI)				
3 months	90.6 (87.1, 94.0)	80.8 (74.1, 87.4)	88.1 (85.1, 91.1)	68.8 (62.8, 74.9)
6 months	69.5 (64.0, 74.9)	54.1 (45.7, 62.5)	60.4 (55.9, 64.9)	41.5 (35.0, 48.0)
9 months	51.3 (45.4, 57.3)	34.7 (26.5, 42.9)	41.1 (36.4, 45.8)	28.2 (22.1, 34.3)
12 months	34.3 (28.1, 40.4)	18.0 (10.5, 25.4)	27.8 (23.0, 32.6)	23.2 (17.1, 29.2)
18 months	18.3 (11.8, 24.9)	9.0 (2.1, 15.9)	8.3 (2.3, 14.2)	10.3 (3.9, 16.8)
Duration (months) of follow-up				
Median (95% CI)	13.31 (–)	13.24 (–)	11.3 (10.6, 12.4)	11.2 (9.9, 12.0)
Comparison (fruquintinib vs placebo)				
Stratified HR (95%CI)†/(SE)‡	0.65 (0.51, 0.83)		0.66 (0.10)	
95% CI‡	–		(0.55, 0.80)	
p-value of stratified log-rank test†/two-sided p-value‡	<0.001		<0.001	

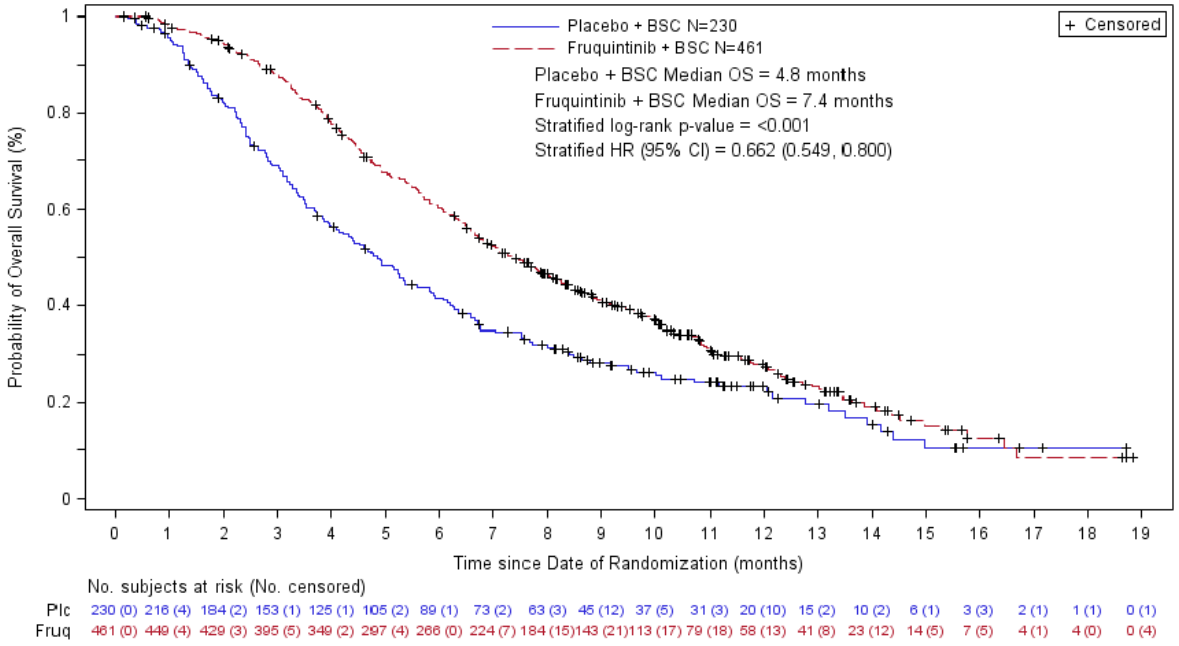
Source: FRESCO final CSR (86) , FRESCO-2 final CSR (93).
†FRESCO only; ‡FRESCO-2 only.
Abbreviations: BSC, best supportive care; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; SE, standard error.

Figure 5: OS Kaplan-Meier curves – FRESCO, ITT population



Source: FRESCO final CSR (86).
Abbreviations: BSC, best supportive care; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.

Figure 6: OS Kaplan-Meier curves – FRESCO-2, ITT population



Source: FRESCO-2 final CSR (93).
Abbreviations: BSC, best supportive care; CSR, clinical study report; ITT, intention-to-treat; OS, overall survival.

B.2.6.2.2 Secondary endpoints

B.2.6.2.2.1 Key secondary endpoint: PFS

Both FRESCO and FRESCO-2 met their key secondary endpoints of PFS, with statistically significant improvements observed with fruquintinib vs placebo.

FRESCO: A total of 235 patients (84.5%) in the fruquintinib arm and 125 patients (90.6%) in the placebo arm experienced PD or death. Median PFS was 1.9 months longer with fruquintinib compared with placebo (3.7 vs 1.8 months) with an HR of 0.26 (95% CI: 0.21, 0.34; p<0.001), indicating that the risk of disease progression or death in the fruquintinib arm was reduced by 74% compared with placebo (Table 12). The KM curves showed a clear separation in favour of fruquintinib (Figure 7) and reflected the marked difference in PFS rates, particularly noticeable at 3 months (63.0% with fruquintinib vs 11.3% with placebo).

FRESCO-2: A total of 392 patients (85.0%) in the fruquintinib arm and 213 patients (92.6%) in the placebo arm experienced PD or death. Similar to FRESCO, median PFS in FRESCO-2 was also 1.9 months longer with fruquintinib compared with placebo (3.7 vs 1.8 months), with an HR of 0.32 (95% CI: 0.27, 0.39; p<0.001), indicating that the risk of disease progression or death in the fruquintinib arm was reduced by 68% compared with placebo (Table 12). The KM curves showed a clear separation in favour of fruquintinib (Figure 8) and reflected the marked difference in PFS rates, particularly noticeable at 3 months (59.6% with fruquintinib vs 17.9% with placebo).

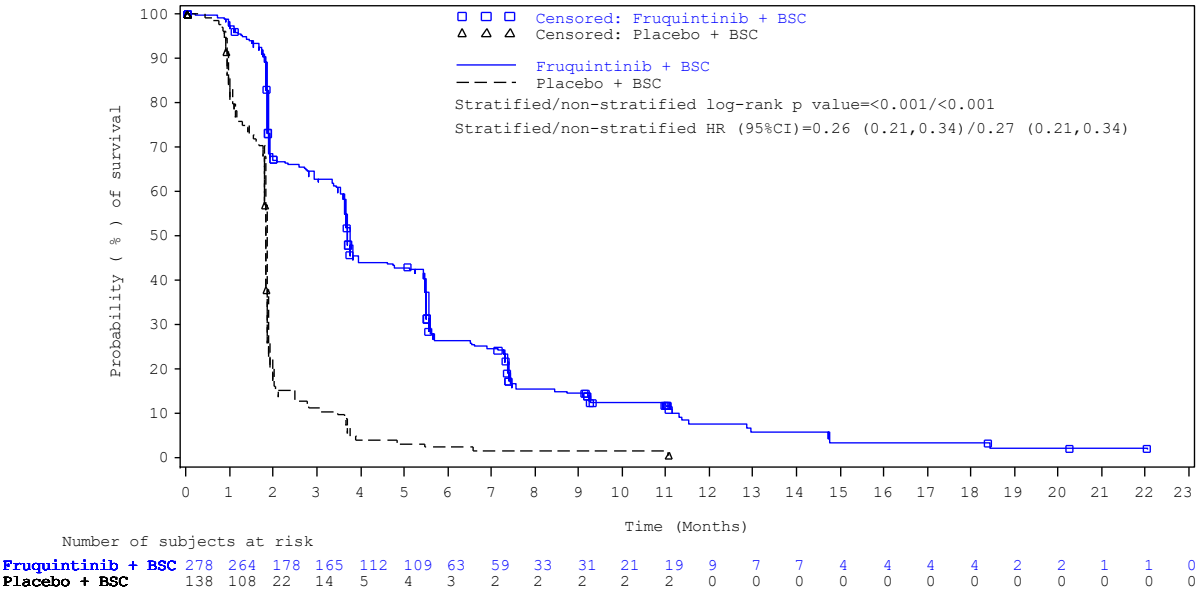
Table 12: Summary of PFS – FRESCO and FRESCO-2, ITT population

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230
No. of patients who died or had PD, n (%)	235 (84.5)	125 (90.6)	392 (85.0)	213 (92.6)
No. of patients who had PD	214 (77.0)	110 (79.7)	301 (65.3)	167 (72.6)
No of patients who died	21 (7.6)	15 (10.9)	91 (19.7)	46 (20.0)
No. of patients censored, n (%)	43 (15.5)	13 (9.4)	69 (15.0)	17 (7.4)
Censoring reasons, n (%)				
No baseline or postbaseline assessment	0	0	17 (24.6)	7 (41.2)
Lost to follow-up without death or PD	–	–	1 (1.4)	0
Withdrawal of consent without death or PD	–	–	4 (5.8)	1 (5.9)
New anti-tumour therapy started prior to death or PD	8 (2.9)	4 (2.9)	10 (14.5)	3 (17.6)
No tumour assessment in the study, no death within 118 days of randomisation	5 (1.8)	6 (4.3)	–	–
Death or PD occurred after ≥ 2 consecutive missed assessments	–	–	0	0

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=138**	**Fruquintinib + BSC N=461**	**Placebo + BSC N=230**
No death or PD by the time of data cutoff for final analysis	21 (7.6)	1 (0.7)	37 (53.6)	6 (35.3)
PFS (months)				
Median (95% CI)	3.71 (3.65, 4.63)	1.84 (1.81, 1.84)	3.7 (3.5, 3.8)	1.8 (1.8, 1.9)
Probability (%) of being alive and progression free at: (95% CI)				
1 month	97.4 (95.5, 99.3)	83.7 (77.3, 90.1)	–	–
3 months	63.0 (57.2, 68.8)	11.3 (5.80, 16.9)	59.6 (55.0, 64.2)	17.9 (12.7, 23.0)
6 months	26.4 (21.0, 31.9)	2.4 (0.0, 5.1)	23.8 (19.7, 28.0)	1.1 (0.0, 2.6)
9 months	–	–	11.3 (8.1, 14.6)	0.5 (0.0, 1.6)
12 months	–	–	3.8 (1.6, 5.9)	0
18 months	–	–	2.1 (0.4, 3.8)	0
Comparison (fruquintinib vs placebo)				
Stratified HR (95%CI)†/(SE)‡	0.26 (0.21, 0.34)		0.32 (0.09)	
95% CI‡	–		0.27, 0.39	
p-value of stratified log-rank test†/two-sided p-value‡	<0.001		<0.001	

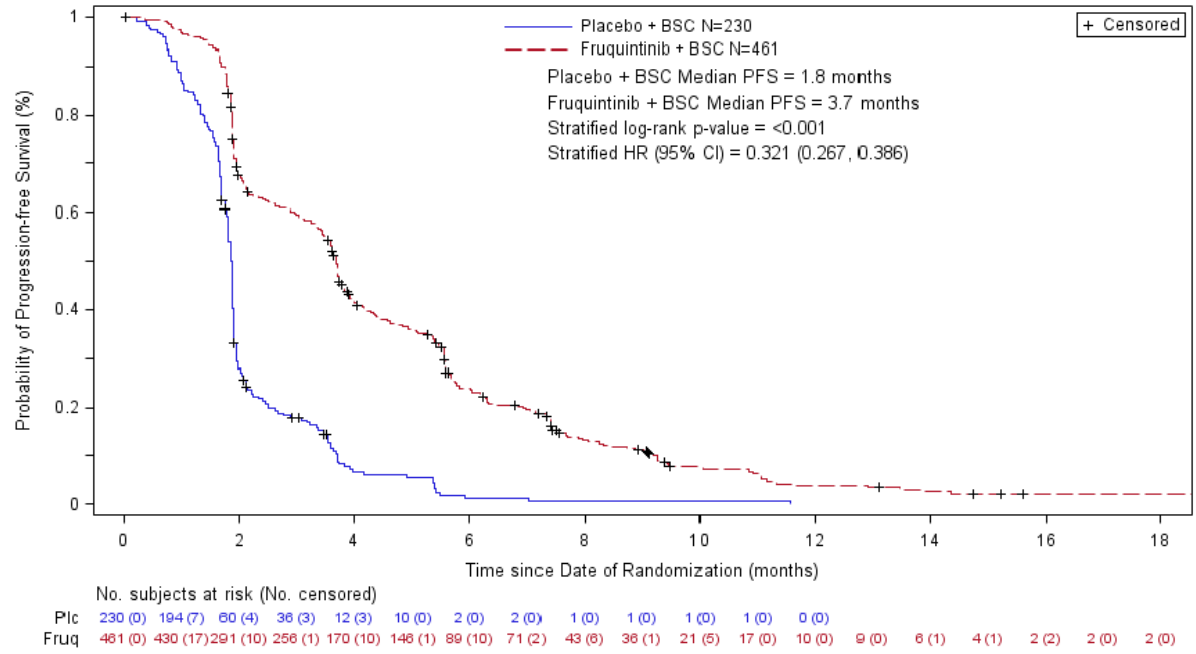
Source: FRESCO final CSR (86), FRESCO-2 final CSR (93).
†FRESCO only; ‡FRESCO-2 only.
Abbreviations: BSC, best supportive care; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; ITT, intention-to-treat; PD, progressive disease; PFS, progression-free survival; SE, standard error.

Figure 7: PFS Kaplan-Meier curves – FRESCO, ITT population



Source: FRESCO Final CSR (86).
Abbreviations: BSC, best supportive care; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Figure 8: PFS Kaplan-Meier curves – FRESCO-2, ITT population



Source: FRESCO-2 final CSR (93).
Abbreviations: BSC, best supportive care; CSR, clinical study report; ITT, intention-to-treat; PFS, progression-free survival.

B.2.6.2.2.2 Other secondary endpoints: BOR, ORR and DCR

FRESCO: The objective response rate (ORR) was significantly higher in the fruquintinib arm than in the placebo arm (4.7% vs 0%, p=0.012). In the fruquintinib arm, one patient (0.4%) had a best overall response (BOR) of complete response (CR), 12 patients (4.3%) had a

partial response (PR), 160 patients (57.6%) had stable disease and 87 patients (31.3%) had progressive disease (PD). None of the patients in the placebo arm had a CR or PR. The DCR, which is acknowledged by oncologists to be a highly clinically relevant endpoint in this patient population, was significantly higher in the fruquintinib arm than in the placebo arm (62.2% vs 12.3%, p<0.001) (Table 13). As the percentage of patients in the fruquintinib arm who experienced PD after achieving objective response was less than 50%, and the patient with the longest duration of objective response was censored as of the final DCO, the median duration of response (DOR) could not be estimated. Instead, the median duration of stable disease was estimated and was found to be longer in the fruquintinib arm (5.5 months, 95% CI: 5.5, 5.6), than in the placebo arm (3.7 months, 95% CI: 3.7, 4.8).

FRESCO-2: The ORR was 1.5% in the fruquintinib arm and 0% in the placebo arm (p=0.059). In the fruquintinib arm, no patient had a CR, seven patients (1.5%) had a BOR of PR, 249 patients (54.0%) had stable disease and 139 patients (30.2%) had PD. None of the patients in the placebo arm had a CR or PR (Table 13). The DCR was significantly higher in the fruquintinib arm than in the placebo arm (55.5% vs 16.1%; p<0.001) (Table 13). The median DOR was 10.7 months (95% CI: 3.9–not estimable [NE]) for patients in the fruquintinib arm and NE for the placebo arm (Table 13).

Table 13: Summary of BOR, ORR and DCR – FRESCO and FRESCO-2, ITT population

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=138**	**Fruquintinib + BSC N=461**	**Placebo + BSC N=230**
BOR, n (%)				
CR	1 (0.4)	0	0	0
PR	12 (4.3)	0	7 (1.5)	0
Stable disease	160 (57.6)	17 (12.3)	249 (54.0)	37 (16.1)
CR – unconfirmed	–	–	0	0
PR – unconfirmed	–	–	5 (1.1)	0
PD	87 (31.3)	98 (71.0)	139 (30.2)	143 (62.2)
NE	18 (6.5)	23 (16.7)	6 (1.3)	1 (0.4)
NA	–	–	60 (13.0)	49 (21.3)
ORR: CR + PR, n (%)	13 (4.7)	0	7 (1.5)	0
Exact 95% CI†/two-sided 95% CI‡	2.51, 7.86	0.00, 2.64	0.6, 3.1	0.0, 1.6
Odds ratio (95%CI)†	– (1.997, –)		–	
Adjusted difference (fruquintinib – placebo) (SE)‡	–		1.5 (0.006)	
95% CI‡	–		0.4, 2.7	

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=138**	**Fruquintinib + BSC N=461**	**Placebo + BSC N=230**
Two-sided p-value†/p-value of exact test‡	0.012		0.059	
DCR: CR + PR + stable disease for at least 7 weeks, n (%)	173 (62.2)	17 (12.3)	256 (55.5)	37 (16.1)
Exact 95%CI†/two-sided95% CI‡	56.25, 67.95	7.34, 18.99	50.9, 60.1	11.6, 21.5
Odds ratio (95%CI)†				
Adjusted difference (fruquintinib – placebo) (SE)‡	–		39.4 (0.034)	
95% CI‡	–		32.8, 46.0	
Two-sided p-value†/p-value of CMH test‡	<0.001		<0.001	
DOR, months				
25th percentile (95% CI)	–	–	10.7 (3.9, NE)	–
Median (95% CI)	–	–	10.7 (3.9, NE)	–
75th percentile (95% CI)	–	–	NE (10.7, NE)	–
Min, max	–	–	2.1, 16.9	–

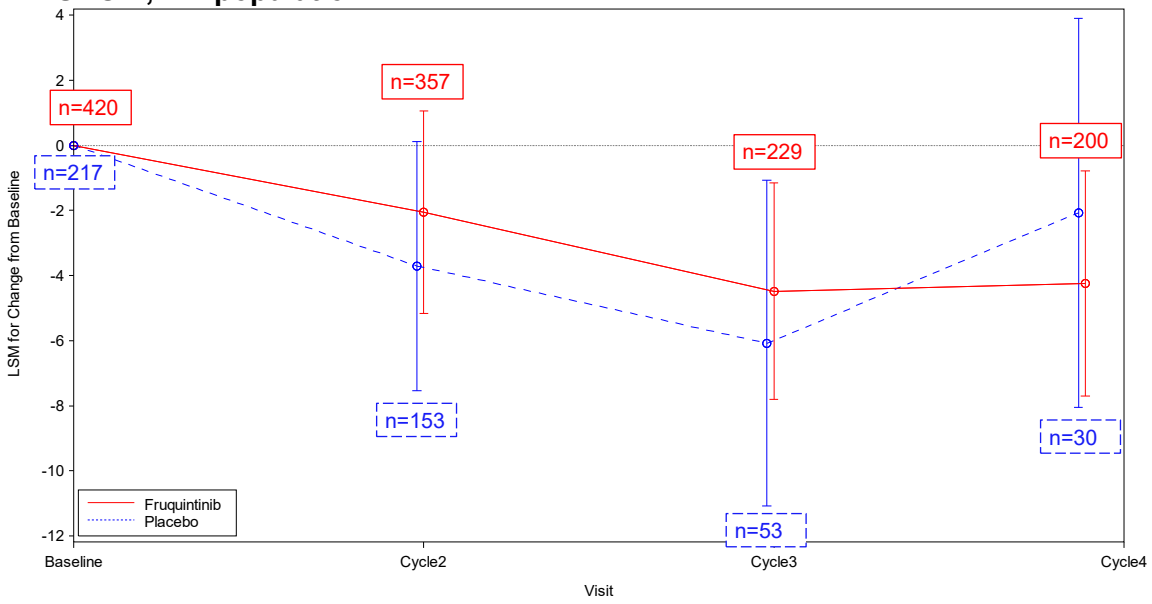
Source: FRESCO final CSR (86), FRESCO-2 final CSR (93).
†FRESCO only; ‡FRESCO-2 only.
Abbreviations: BOR, best overall response; BSC, best supportive care; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CR, complete response; CSR, clinical study report; DCR, disease control rate; DOR, duration of response; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PR, partial response; SE, standard error.

B.2.6.2.3 Patient-reported outcomes: FRESCO-2

Patients with mCRC experience decreased HRQoL with each additional line of therapy they receive (14) and therefore maintaining the best possible HRQoL, while prolonging survival, is one of the main aims of treatment in this setting (15). HRQoL was assessed in FRESCO-2 only, from patients in the ITT population with non-missing baseline and at least one non-missing post-baseline assessment results. Data on HRQoL were collected using the European Organisation for Research and Treatment of Cancer – Core Quality of Life (EORTC QLQ-C30) and EQ-5D five-level (EQ-5D-5L) questionnaires, as described in Appendix M. Assessments of QLQ-C30 and EQ-5D-5L were conducted at baseline and on Day 1 of subsequent treatment cycles. Consistent with the number of patients who remained on treatment over time, the completion rate for both questionnaires in each cycle progressively decreased over time, with the rate of decrease greater in patients in the placebo arm vs the fruquintinib arm. The questionnaire completion rate at baseline and in each cycle was based on the total number of patients who entered the cycle and who were expected to complete the questionnaire; the completion rate was maintained at greater than 80% in the two treatment arms over time.

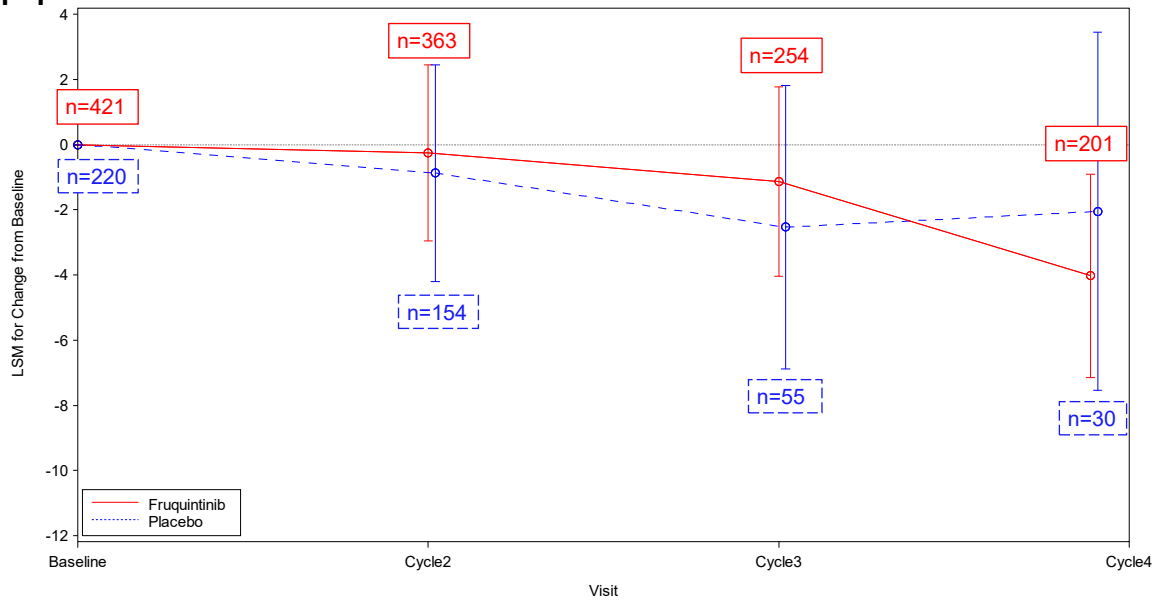
For QLQ-C30 global health status and EQ-5D-5L visual analogue scale (VAS), the scores at baseline were similar between the fruquintinib and placebo arms. The least squares mean (LSM) change from baseline scores based on both instruments demonstrated that patients in the fruquintinib arm tended to have a slower worsening in clinical condition vs patients in the placebo arm (Figure 9 and Figure 10). In addition, the LSM difference between fruquintinib and placebo for the LSM change from baseline results for Cycle 2 and Cycle 3 for the QLQ-C30 global health status and EQ-5D-5L VAS score showed a trend towards a benefit in patients treated with fruquintinib vs those treated with placebo (Figure 11).

Figure 9: Least squares mean change from baseline: QLQ-C30 Global Health Status – FRESCO-2, ITT population



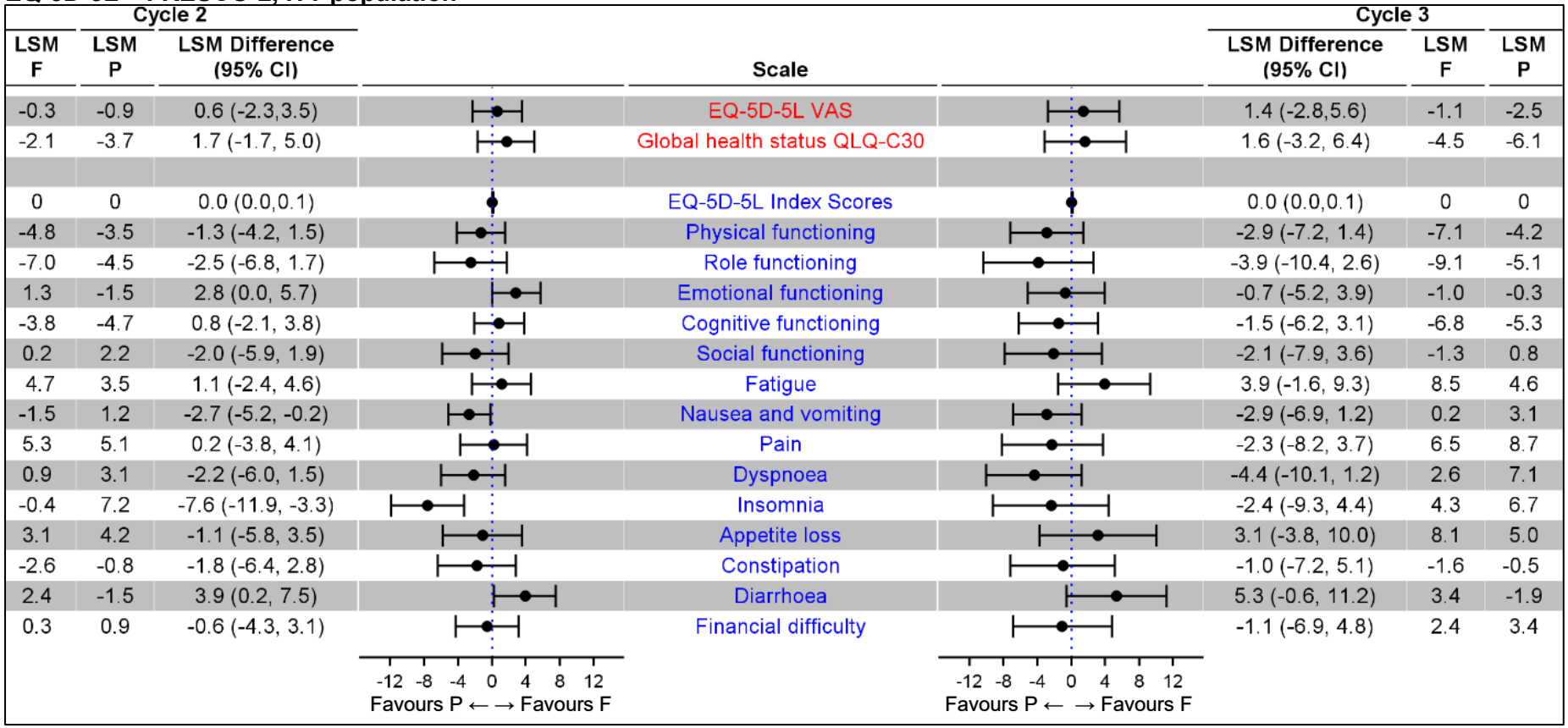
Source: FRESCO-2 figures (115).
Abbreviations: ITT, intention-to-treat; LSM, least squares mean; QLQ-C30, Core Quality of Life questionnaire.

Figure 10: Least squares mean change from baseline: EQ-5D-5L VAS – FRESCO-2, ITT population



Source: FRESCO-2 figures (115).
Abbreviations: EQ-5D-5L, EuroQol five-dimension five-level; ITT, intention-to-treat; LSM, least squares mean; VAS, visual analogue score.

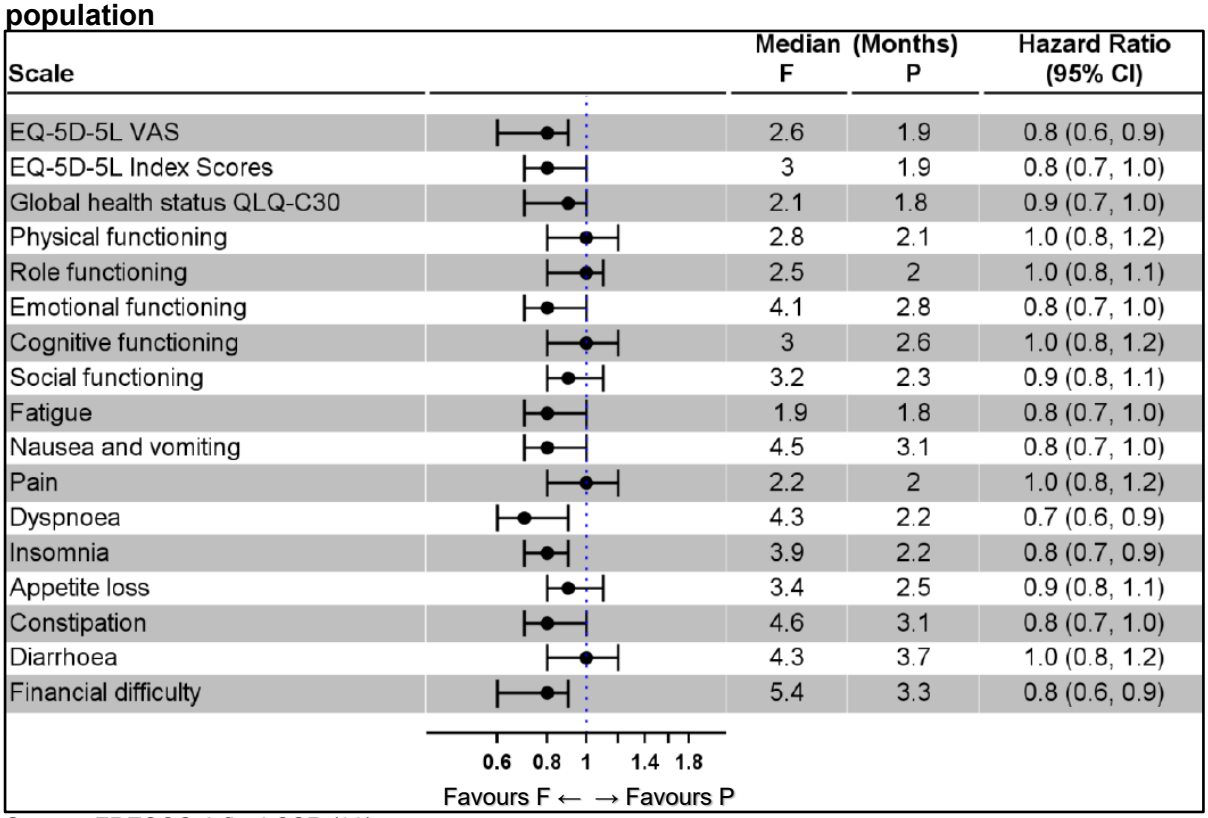
Figure 11: Forest plot for LSM difference between fruquintinib and placebo for QLQ-C30 Global Health Status, QLQ-C30 subscales, and EQ-5D-5L – FRESCO-2, ITT population



Source: FRESCO-2 final CSR (93).
Abbreviations: CSR, clinical study report; EQ-5D-5L, EuroQol five-dimension five-level; F, fruquintinib; ITT, intention-to-treat; LSM, least squares mean; P, placebo; QLQ-C30, Core Quality of Life questionnaire; VAS, visual analogue score.

The median time-to-deterioration, and the corresponding HRs for all scales and subscales, showed a trend favouring fruquintinib, suggesting that treatment with fruquintinib delayed the risk of deterioration in the quality of life of patients vs placebo (Figure 12).

Figure 12: Forest plot for hazard ratio (fruquintinib vs placebo) of time to deterioration for QLQ-C30 global health, QLQ-C30 subscales and EQ-5D-5L – FRESCO-2, ITT population



Source: FRESCO-2 final CSR (93).
Abbreviations: CSR, clinical study report; EQ-5D-5L, EuroQol five-dimension five-level; F, fruquintinib; ITT, intention-to-treat; LSM, least squares mean; P, placebo; QLQ-C30, Core Quality of Life questionnaire; VAS, visual analogue score.

Taken together, HRQoL as measured by QLQ-C30 and EQ-5D-5L was not negatively impacted by treatment with fruquintinib. Overall, and importantly, fruquintinib delayed time-to-deterioration in patients' HRQoL compared with placebo, and the benefit in patients treated with fruquintinib was consistent across most subscales.

B.2.6.3 Pooled analysis of FRESCO and FRESCO-2

B.2.6.3.1 Rationale and methods

As described in Section B.2.3.3 and B.2.5, advisors at the UK oncologist advisory board (22nd September 2023) stated that both FRESCO and FRESCO-2 offer strong and compelling data packages that complement each other well, that both trials are highly relevant for clinical decision-making for the population of interest, and that together, they

comprise an evidence base generalisable to the UK patient population (8). Based on this feedback, individual patient data for the ITT populations of FRESCO and FRESCO-2 were pooled to inform the majority of clinical inputs in the economic model. This was considered the best use of the available evidence base as this approach:

- Utilises both large, blinded, Phase III RCTs that assessed fruquintinib vs BSC in the population of interest
- Reflects a population that is more representative of the UK landscape vs using FRESCO or FRESCO-2 independently (described further below)
- Provides a greater sample size to inform analyses, and hence reduces uncertainty in clinical inputs in the economic model
- Aligns with the approach conducted in TA866 and TA405 (7, 55), and specifically the NICE committee preferences in both appraisals.

Importantly, both studies were considered comparable with respect to study design and endpoint definitions, population (i.e. patients who had received at least two prior lines of systemic therapy for mCRC), and patient baseline characteristics, including age, BMI, percentage of patients with liver metastases, primary tumour location at first diagnosis, stage of disease and gender.

As described in Section B.2.3.3 and B.2.5, advisors at the UK oncologist advisory board (22nd September 2023) stated that FRESCO is considered more representative of the UK population's current low rate of exposure to anti-VEGF treatments (e.g. bevacizumab), while FRESCO-2 is considered more representative of the UK population with respect to ethnicity (11). Pooling an Asian-only and a global study together also aligns with the approach conducted in TA866 and TA405. Based on this and the discussion in Section B.2.5, it was concluded that the observed imbalances in ethnicity and prior anti-VEGF exposure should not prohibit pooling the data.

The pooled analysis combined the individual patient data from the ITT populations of FRESCO and FRESCO-2. Endpoints were defined consistently across the two trials and therefore no adjustments were made. The following endpoints in the economic model were informed by this pooled analysis, unless otherwise stated: OS, PFS, and time to treatment discontinuation (TTD) for fruquintinib, OS and PFS for BSC, AE rates, fruquintinib RDI and

subsequent therapies. The pooled analysis was also used to inform modelled patient baseline characteristics; bodyweight, body surface area (BSA), age and % male.

B.2.6.3.2 Demographics and baseline characteristics

Pooled patient demographics and baseline characteristics are presented in Table 14. Of note, both FRESCO and FRESCO-2 were assessed as having low risk of bias using the Cochrane RoB tool (Section B.2.5 and Appendix D).

Table 14: Summary of patient demographics and baseline characteristics – pooled FRESCO and FRESCO-2, ITT population

	Fruquintinib + BSC N=739	Placebo + BSC N=368	Total N=1107
Age (years)			
n	739	368	1107
Mean (SD)	59.2 (11.17)	59.7 (10.60)	59.4 (10.98)
Median (Q1, Q3)	61 (52.0, 68.0)	62 (53.0, 66.0)	61 (52.0, 67.0)
Min, Max	23, 82	24, 86	23, 86
Age group 1, n (%)			
<65	475 (64.3)	229 (62.2)	704 (63.6)
≥65	264 (35.7)	139 (37.8)	403 (36.4)
Age group 2, n (%)			
<65	229 (62.2)	475 (64.3)	704 (63.6)
≥65 to <74	116 (31.5)	206 (27.9)	322 (29.1)
≥74 to <85	22 (6.0)	58 (7.8)	80 (7.2)
≥85	1 (0.3)	0	1 (0.1)
Gender, n (%)			
Male	403 (54.5)	237 (64.4)	640 (57.8)
Female	336 (45.5)	131 (35.6)	467 (42.2)
Ethnicity, n (%)			
Hispanic or Latino	20 (2.7)	14 (3.8)	34 (3.1)
Not Hispanic or Latino	683 (92.4)	340 (92.4)	1023 (92.4)
Not reported/Unknown	36 (4.9)	14 (3.8)	50 (4.5)
Region group 1, n (%)			
China	278 (37.6)	138 (37.5)	416 (37.6)
Non-China	461 (62.4)	230 (62.5)	691 (62.4)
Region group 2, n (%)			
USA	82 (11.1)	42 (11.4)	124 (11.2)
Non-USA	657 (88.9)	326 (88.6)	983 (88.8)

	Fruquintinib + BSC N=739	Placebo + BSC N=368	Total N=1107
Region group 3, n (%)			
North America	82 (11.1)	42 (11.4)	124 (11.2)
Europe	329 (44.5)	166 (45.1)	495 (44.7)
Australia	10 (1.4)	6 (1.6)	16 (1.4)
Asia	318 (43.0)	154 (41.8)	472 (42.6)
Race category 1, n (%)			
American Indian or Alaskan native	0	1 (0.3)	1 (0.1)
Asian	321 (43.4)	156 (42.4)	477 (43.1)
Black or African American	13 (1.8)	7 (1.9)	20 (1.8)
Native Hawaiian or other Pacific Islander	3 (0.4)	2 (0.5)	5 (0.5)
White	367 (49.7)	192 (52.2)	559 (50.5)
Other	5 (0.7)	2 (0.5)	7 (0.6)
Multiple race	2 (0.3)	0	2 (0.2)
Not reported/Unknown	28 (3.8)	8 (2.2)	36 (3.3)
Race category 2, n (%)			
White	367 (49.7)	192 (52.2)	559 (50.2)
Asian	321 (43.4)	156 (42.4)	477 (43.1)
Black or African American	13 (1.8)	7 (1.9)	20 (1.8)
Other	38 (5.1)	13 (3.5)	51 (4.6)
Race category 3, n (%)			
White	367 (49.7)	192 (52.2)	559 (50.5)
Non-white	372 (50.3)	176 (47.8)	548 (49.5)
Height (cm)			
n	729	363	1092
Mean (SD)	167.06 (8.957)	167.76 (8.647)	167.29 (8.857)
Median (Q1, Q3)	167 (160, 173)	168 (162, 174)	168 (160, 173)
Min, Max	141.5, 195.5	143, 197	141.5, 197
Weight (kg)			
n	730	365	1095
Mean (SD)	69.95 (15.753)	70.61 (16.671)	70.17 (16.060)
Median (Q1, Q3)	68 (59.60, 78.50)	69.20 (59.0, 80.0)	68 (59.0, 79.0)
Min, Max	40.0, 158.2	40.0, 144.2	40.0, 158.2
BMI (kg/m)			
n	728	363	1091
Mean (SD)	24.929 (4.7353)	24.912 (4.7422)	24.924 (4.7354)

	Fruquintinib + BSC N=739	Placebo + BSC N=368	Total N=1107
Median (Q1, Q3)	24.231 (21.675, 27.356)	24.353 (21.551, 27.734)	24.281 (21.644, 27.445)
Min, Max	16.02, 56.72	15.63, 49.43	15.63, 56.72
BMI categories, n (%)			
<18.5	43 (5.8)	22 (6.0)	65 (5.9)
≥18.5 to <24	299 (40.5)	146 (39.7)	445 (40.2)
≥24	386 (52.2)	195 (53.0)	581 (52.5)
Missing	11 (1.5)	5 (1.4)	16 (1.4)
BSA, m^2			
n	728	363	1091
Mean (SD)	1.78 (0.214)	1.79 (0.221)	1.78 (0.216)
Median	1.76	1.79	1.77
Min, Max	1.26, 2.53	1.32, 2.62	1.26, 2.62
ECOG performance status, n (%)			
0	273 (36.9)	139 (37.8)	412 (37.2)
1	466 (63.1)	229 (62.2)	695 (62.8)

Source: FRESCO and FRESCO-2 pooled data (116).
Abbreviations: BMI, body mass index; BSA, body surface area; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; Q, quartile; SD, standard deviation; USA, United States of America.

B.2.6.3.3 Efficacy

A detailed summary of pooled OS and PFS results are presented in Appendix N. A total of 505 patients (68.3%) in the fruquintinib arm and a total of 282 patients (76.6%) in the placebo arm had died by the end of follow up. Two hundred and thirty-four patients (31.7%) in the fruquintinib arm and 86 patients (23.4%) in the placebo arm were still alive at the end of follow up. As outlined in Figure 13, median OS was 8.02 months with fruquintinib vs 5.55 months with placebo (i.e. an OS benefit of 2.5 months with fruquintinib), with an HR of 0.66 (95% CI: 0.57, 0.76; p<0.0001), indicating that the risk of death in the fruquintinib arm was reduced by 34% vs placebo.

In terms of PFS, 627 patients (84.8%) in the fruquintinib arm and 338 patients (91.8%) in the placebo arm had experienced PD or death by the end of follow up. As outlined in Figure 14, median PFS was 1.87 months longer with fruquintinib vs placebo (3.71 vs 1.84 months) with an HR of 0.31 (95% CI: 0.27, 0.36; p<0.0001 indicating that the risk of disease progression or death in the fruquintinib arm was reduced by 69% vs placebo.

Overall, the results of the pooled analysis for both PFS and OS are consistent with the individual studies, FRESCO and FRESCO-2.

Figure 13: OS Kaplan-Meier curves – Pooled analysis, ITT population

Source: FRESCO and FRESCO-2 pooled data (116).
Abbreviations: BSC, best supportive care; CI, confidence interval; ITT, intention-to-treat; OS, overall survival.

Figure 14: PFS Kaplan-Meier curves – Pooled analysis, ITT population

Source: FRESCO and FRESCO-2 pooled data (116).
Abbreviations: BSC, best supportive care; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival.

B.2.7 Subgroup analysis

In FRESCO and FRESCO-2, prespecified subgroup analyses were performed for OS and PFS. In both FRESCO and FRESCO-2, OS and PFS results across most prespecified subgroups were consistent with those of the primary analyses, and favoured fruquintinib over placebo. A summary of the results for the subgroups is presented in Appendix E.

FRESCO: Overall, OS and PFS results across different subgroups were consistent with the primary analysis. A consistent improvement in OS and PFS favouring the fruquintinib arm was observed across most prespecified subgroups. In the OS subgroup analysis by prior anti-VEGF therapy, a trend towards an improved treatment effect was seen in the subgroup of patients with no prior anti-VEGF use: a numerically less favourable HR was reported in patients who had been treated with a prior anti-VEGF therapy (0.68, CI: 0.45–1.03) compared with patients who had not (0.60, CI: 0.45–0.80). As discussed in Section B.2.6.3.1, prior exposure to anti-VEGF therapy may reduce the treatment effect of other therapies with anti-VEGF activity, such as fruquintinib, given the mechanism of action targets some of the same anti-angiogenic pathways (18).

FRESCO-2: A consistent improvement in OS favouring the fruquintinib arm was observed across prespecified subgroups including age, number of prior lines of therapy in metastatic disease, prior therapy, *RAS* mutation, duration of metastatic disease, and liver metastasis. Similar to OS, an improvement in PFS favouring fruquintinib was consistently observed across all prespecified subgroups.

B.2.8 Meta-analysis

Meta-analyses of HRs for OS and PFS from FRESCO and FRESCO-2 were conducted. Fixed effects (FE) and random effects (RE) models with the inverse variance method for pooling were fitted. Contrast-level data were used as inputs (i.e. log-hazard ratios and their standard errors [SEs]). Analyses were conducted using the *meta* package in R.

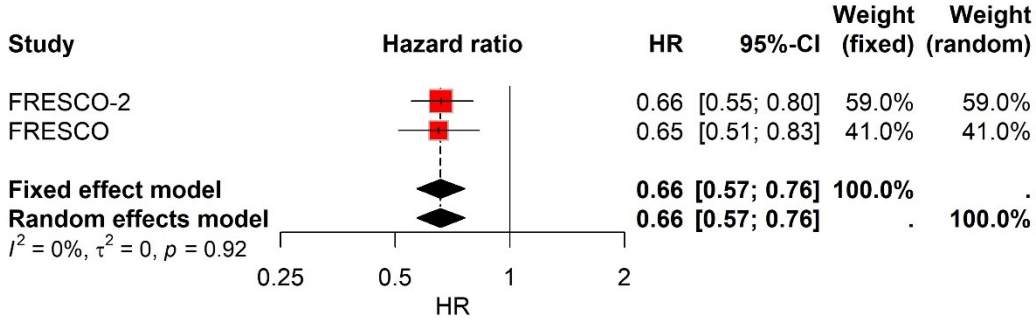
Heterogeneity for each comparison was assessed through the between-study variance, τ^2, estimated using the restricted maximum-likelihood estimator (REML); values of τ^2 between 0.0000 to 0.0201 indicate low between-study variance (117). Additionally, heterogeneity was assessed by calculating I^2, an estimate of the percentage of variability due to heterogeneity. An I^2 value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Typically, I^2 values of 25%, 50%, and 75% are considered low, moderate, and high heterogeneity, respectively (118). Finally, the Cochrane's Q-test for heterogeneity was conducted to test the null hypothesis that the true treatment effects are the same in both studies included in the MA. With a small number of studies (<20), the Q test should be interpreted very cautiously (119). A p-value < 0.05 indicates the null hypothesis should be rejected at a 95% confidence level and that there is statistical heterogeneity between the studies.

Results for OS and PFS are presented in Figure 15 and Figure 16, respectively. The HRs estimated by the meta-analyses for OS and PFS for fruquintinib vs placebo were consistent between the FE and RE models. The FE HRs were 0.66 (95% CI: 0.57, 0.76) and 0.30 (95% CI: 0.26, 0.34) for OS and PFS for OS and PFS, respectively, and the RE HRs were, respectively. These results align with the pooled relative efficacy outcomes presented in Section B.2.6.3.3 (and Appendix D).

For OS, the HRs from FRESCO and FRESCO-2 are very similar, with overlapping 95% CIs. The p-value for the Q-test was 0.92, indicating no evidence of statistical heterogeneity between the studies. The between-study variance τ^2 was 0 and the I^2 statistic was estimated at 0%, which are also indicators of no evidence of statistical heterogeneity between the results of FRESCO and FRESCO-2. These low values of statistical heterogeneity can be explained by the FRESCO-2 HR point estimate and 95% CI lying entirely within the range of the 95% CI around the FRESCO HR.

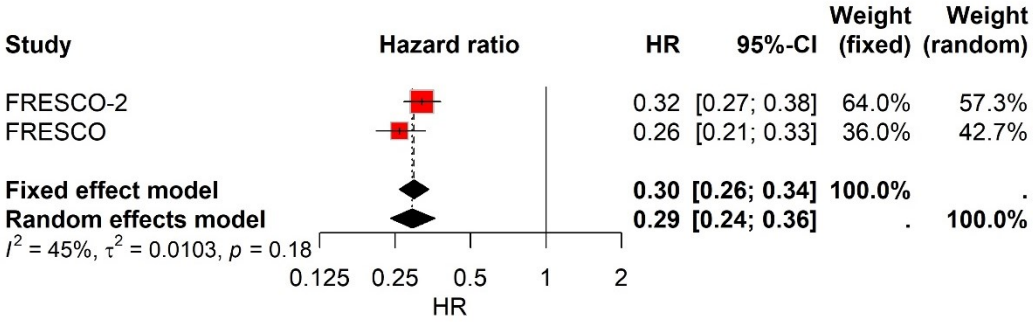
For PFS, there is slight variation in the point estimate HRs between FRESCO and FRESCO-2, however, the 95% CIs overlap. The I^2 statistic was estimated at 45%, indicating a moderate level of statistical heterogeneity between the studies may be present. Further, the between-study variance was low at 0.01 (117), and the p-value for the Q-test was 0.18. While this p-value is smaller than that for OS, it remains >0.05, indicating a lack of statistical heterogeneity between the studies. These moderate values of the heterogeneity statistics can be explained by the FRESCO-2 HR point estimate lying within the range of the CIs around the FRESCO HR but the FRESCO HR lying outside of the range of CIs around the FRESCO 2 HR.

Figure 15: OS: pairwise meta-analysis results



I^2The percentage of variance in the estimates beyond that expected due to chance (degree of heterogeneity); τ^2Between;-study variance (assumed 0 under fixed-effect model); p-value in Cochrane's Q test of homogeneity.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Figure 16: PFS: pairwise meta-analysis results



I^2The percentage of variance in the estimates beyond that expected due to chance (degree of heterogeneity); τ^2Between;-study variance (assumed 0 under fixed-effect model); p-value in Cochrane's Q test of homogeneity.
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Summary of approach

In the absence of direct head-to-head evidence comparing the efficacy of fruquintinib with trifluridine-tipiracil or regorafenib, a network meta-analysis (NMA) was conducted to synthesise relative treatment effects for OS and PFS in line with the recommendations in the NICE Decision Support Unit (DSU) technical support document (TSD) 2 (120) and NICE DSU TSD 18 (121).

The clinical efficacy of fruquintinib, regorafenib, trifluridine-tipiracil and placebo was identified through a clinical SLR that identified all available randomised evidence evaluating the efficacy and safety of fruquintinib and relevant comparators with or without BSC for the treatment of patients with previously treated mCRC, as described in Section B.2.1 and Appendix D. Eight of the RCTs identified by the SLR met the inclusion criteria for the NMA and connected in a star-shaped network (Section B.2.9.2). In the network, direct evidence for all treatments (active treatment ± BSC) was against placebo ± BSC (hereafter referred to as BSC).

The use of an NMA is consistent with guidance from NICE Technical Support Document (TSD) 18, which specifies that randomised studies that form a connected network should be analysed via NMA when there is no clear evidence of effect modification (121). Potential treatment effect modifiers were identified based on an assessment of clinical trial subgroup data (including observed interaction tests where available), clinical expert opinion elicited at a the UK market access advisory board (1st December 2023) (47), and evidence from TA405 (55) and TA866 (7). However, based on opinion from clinical and health economics experts

elicited at the UK market access advisory board (1st December 2023), it was advised that adjusting for treatment effect modifiers in this population was not necessary. Nevertheless, it was recommended that subgroup analyses be conducted to explore the impact of any imbalance in potential effect modifiers across included studies on results, and therefore, a series of scenario analyses were conducted to explore uncertainty in the analysis (Section B.2.9.6). Full detail on methods of the NMA is presented in Appendix D (Section D.4)

B.2.9.2 Feasibility assessment

All RCTs reporting PFS and OS data for fruquintinib, regorafenib, trifluridine-tipiracil, or BSC identified by the clinical SLR were considered for inclusion in the NMA; the inclusion criteria are presented in Table 15. In terms of study design, there was a sufficient number of RCTs identified by the SLR to create a network of evidence, therefore only RCTs were considered for inclusion in the NMA, as per TSD 2 guidance (120).

Table 15: NMA study inclusion criteria

	Inclusion criteria
Population	Patients with mCRC who have been previously treated with or are not considered candidates for available therapies†
Interventions	As monotherapy, with placebo, or with BSC: • Fruquintinib • Regorafenib • Trifluridine-tipiracil
Comparators	• Placebo • Best supportive care • Any pharmacologic treatment
Outcomes	• OS • PFS
Study design	RCTs (Phase II, or III)

† Available therapies included fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy.
Abbreviations: BSC, best supportive care; EGFR, epidermal growth factor receptor; ITC, indirect treatment comparison; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; VEGF, vascular endothelial growth factor

Among the 281 primary studies identified by the clinical SLR, 23 were RCTs (as detailed in Section B.2.1 and Appendix D [Section D.2.1]). Eight of these met the NMA inclusion criteria: a summary of these RCTs is provided in Table 16. The study selection process is reported in Appendix D (Section D.3.1) and a list of RCTs identified by the SLR but excluded from the NMA is provided in Appendix D (Section D.3.1, Table 63).

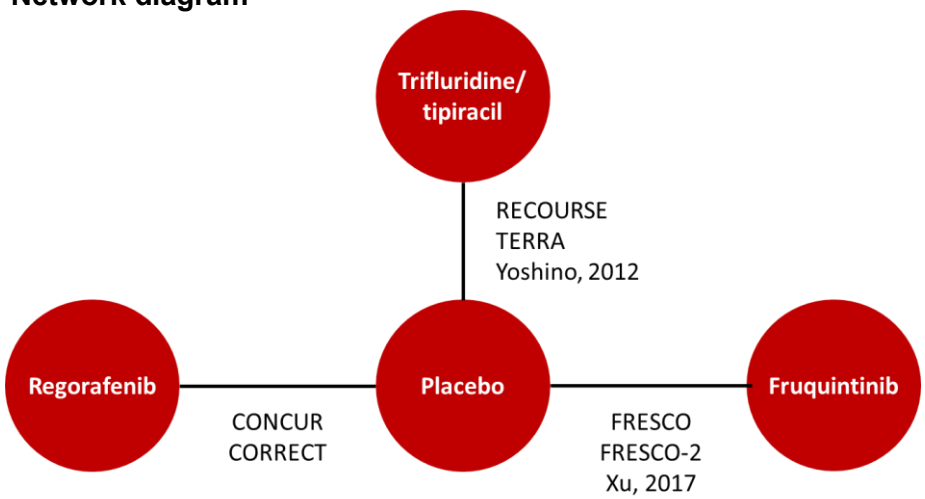
The network diagram is the same for both PFS and OS (Figure 17).

Table 16: RCTs included in the NMA

Trials (references)	Intervention, N	Comparator, N	Phase	Location	Lines of prior treatment (study inclusion criteria)
FRESCO (14, 16, 19, 22, 28)	Fruquintinib + BSC, (n=278)	Placebo + BSC, (n = 138)	III	Asia only	Failure of ≥2 lines of standard chemotherapies for advanced disease
FRESCO-2 (7-10, 12, 20, 23, 30)	Fruquintinib + BSC, (n=461)	Placebo + BSC, (n = 230)	III	Global	Number of lines of prior treatment not specified, inclusion based on receiving all required treatments†
Xu, 2017 (29)(13)	Fruquintinib + BSC, (n=47)	Placebo + BSC, (n = 24)	II	Asia only	Failure of ≥2 lines of standard therapy (not specific to metastatic disease)
CONCUR (6, 15, 27)	Regorafenib + BSC, (n=136)	Placebo + BSC, (n = 68)	III	Asia only	Failure of ≥2 lines of previous treatment (not specific to metastatic disease)
CORRECT (5, 11, 31)	Regorafenib + BSC, (n=505)	Placebo + BSC, (n = 255)	III	Global	Number of lines of prior treatment not specified; inclusion based on receiving all required treatments‡
Yoshino, 2012 (32)	Trifluridine-tipiracil + BSC (n=114)	Placebo + BSC, (n = 58)	II	Asia only	History of ≥2 lines of standard chemotherapy (not specific to metastatic disease)
RECOURSE (17, 18, 25, 33, 34)	Trifluridine-tipiracil + BSC (n=534)	Placebo + BSC, (n = 266)	III	Global	Failure of ≥2 lines of standard chemotherapies for metastatic disease
TERRA (21, 26)	Trifluridine-tipiracil + BSC (n=271)	Placebo + BSC, (n = 135)	III	Asia only	Failure of ≥2 lines of standard chemotherapies for metastatic disease

† The inclusion criterion did not specify the number of prior lines of treatment. All patients in the trial had received ≥2 treatments: 2 prior treatments 0.7%, 3 prior treatments 16.8%, >3 treatments 82.5%
‡ The inclusion criterion did not specify the number of prior lines of treatment. 1–2 prior treatments 26.1% (2% of patients on placebo and 3% on regorafenib had received only one previous line of treatment for metastatic disease), 3 prior treatments 25.9%; ≥4 prior treatments 48.0%
Abbreviations: RCT, randomised controlled trial.

Figure 17: Network diagram†



†Treatments in the network were + BSC

All RCTs considered for inclusion in the NMA were deemed comparable with respect to study design and inclusion/exclusion criteria (Appendix D, Section D.3.1.1.1), endpoint definitions (Appendix D, Section D.3.1.1.2), and treatment dosing (Appendix D, Section D.3.1.1.3). Experts at the UK market access advisory board (1st December 2023) considered any differences minor and not of concern (47): despite variation in trial phases (Phase II vs Phase III), all trials were deemed appropriate for inclusion. Although differences existed in geographic location and prior therapy requirements, they were considered minor and unlikely to substantially influence results. Patient characteristics were broadly comparable between trials (Appendix D, Section D.3.1.1.4), with only minor imbalances identified in prior anti-VEGF/bevacizumab, proportion of Asian patients, ECOG status, presence of liver metastasis, number of metastatic sites and the number of prior lines of therapy (Section B.2.9.3). All eight RCTs were therefore considered appropriate to include in the base case network.

B.2.9.3 Treatment effect modification

Where imbalances in baseline characteristics were identified, an assessment was conducted to determine whether these were potential treatment effect modifiers. In line with TSD18, the assessment included: (i) trial subgroup data in the eight RCTs; (ii) any relevant discussion from prior HTAs on treatment effect modifiers (TA405 and TA866) (134, 47); and (iii) clinical expert opinion elicited at the UK market access advisory board (1st December 2023) (48).

In the review of trial subgroup data, tests for subgroup interactions were used to determine evidence of effect modification where available (122). Specifically, if the interaction test was associated with a significant p-value (i.e. $p \leq 0.05$), the relevant subgroup was considered a potential effect modifier. Only the FRESCO, Yoshino 2012, and TERRA publications reported p-values based on subgroup interaction tests for OS and/or PFS. Therefore, TA866 was consulted, which reported conclusions of potential treatment effect modification based on whether interaction test p-values were <0.1. If TA866 reported a significant interaction test, the relevant subgroup was considered a potential effect modifier. Of note, the relevant HRs and p-values were not reported in TA866, and it was unclear whether their conclusions applied to both OS and PFS. Therefore, based on the information available, the conclusions were assumed to apply to both outcomes (7). As interaction effects and associated p-values were scarcely reported across the included trials, and there is no established methodology for assessing effect modification using subgroup data beyond review of statistical tests for interaction, the available subgroup OS and PFS data were compared to the opposite subgroup data, if available, or ITT population. Specifically, if the HR point estimates, range of

confidence intervals, and/or associated interpretation of the subgroup analysis differed to the opposite subgroup data or ITT analysis, this was considered to indicate that the characteristic may represent a potential treatment effect modifier.

The results of this assessment across the variables considered imbalanced across RCTs (prior anti-VEGF/bevacizumab, proportion of Asian patients, ECOG status, presence of liver metastasis, number of metastatic sites and the number of prior lines of therapy) is provided in Table 17, and full details on the assessment are provided in Appendix D (Section D.3.1.2).

Table 17: Summary of assessment for effect modification

Characteristic	Imbalance observed between RCTs	Conclusion of effect modification assessment				Overall conclusion of effect modification†
		Subgroup data	Clinical opinion	Prior NICE appraisals		
				TA405 (55)	TA866 (7)	
Prior anti-VEGF/ bevacizumab (Yes vs No)	Yes	Indicates larger treatment effects in the subgroup of patients with no prior use of VEGF/ bevacizumab vs the subgroup with prior use of VEGF/bevacizumab (Appendix D, Section D.3.1.2.1)	Yes	No	Yes‡: identified as having stronger evidence for treatment effect modification through assessment of clinical trials (interaction p-values <0.1) and validation of clinicians in the company submission	Likely TEM
Ethnicity (Asian vs non-Asian)	Yes	Evidence suggests potential larger treatment effect for Asian vs non-Asian populations (Appendix D, Section D.3.1.2.1)	No	No	No‡	Possible TEM
ECOG PS (0 vs 1)	Yes	Evidence gave no clear indication of treatment effect modification across trial subgroups (Appendix D, Section D.3.1.2.1)	No	No	No‡	No TEM
Number of metastatic sites	Yes	Evidence suggests potential smaller treatment effects in the subgroup with multiple metastatic sites (Appendix D, Section D.3.1.2.1)	No	No	No‡	Possible TEM
Liver metastases (Yes vs No)	Yes	Evidence suggests potential smaller treatment effects in the subgroup of patients with liver metastases (Appendix D, Section D.3.1.2.1)	Potential¶	No	No‡	Possible TEM
Number of prior lines of therapy for metastatic disease	Yes	Contradicting evidence (Appendix D, Section D.3.1.2.1)	Yes	No	No‡	Possible TEM

†Likely: non-overlapping confidence intervals and/or point estimates with a twofold difference, with consistent evidence for TEM across assessments; Possible: overlapping confidence intervals, but point estimates differing by more than 20%, with limited/contradicting evidence across assessments; No: overlapping confidence intervals, with point estimates showing a 10%-20% difference falling within the intervals, or no evidence across assessments.
‡See Appendix D (Section D.3.1.2.2)
¶Feedback from advisors at the UK market access advisory board (1st December 2023) (47) indicated that the presence of liver metastases may be a potential treatment effect modifier moreso that the number of metastatic sites.
Abbreviations: EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; NICE, National Institute for Health and Care Excellence; PS, performance status; RCT, randomised controlled trial; TEM, treatment effect modifier.

Prior treatment with an anti-VEGF was the only characteristic that was considered a likely treatment effect modifier given there was consistent evidence of effect modification across all three assessments conducted. Other characteristics were regarded as potentially having an impact, or no discernible effect, based on the limited and conflicting evidence available (Table 17). Clinical input confirmed that no other effect modifiers were relevant for this population (47).

However, as discussed in Section B.2.9.1, experts at the UK market access advisory board (1st December 2023) stated it was unnecessary to adjust for treatment effect modifiers at this late line of treatment and that a standard NMA is most appropriate given the poor prognosis of patients at this line of therapy. A series of scenario analyses were conducted to evaluate uncertainty in the NMA and explore the impact of heterogeneity in the distribution of potential treatment effect modifiers between studies on the NMA results (Section B.2.9.6). These results were consistent vs the base case analysis.

B.2.9.4 Statistical analysis

To align with TSD 2 (120), classical REML pairwise meta-analyses of all directly compared interventions were conducted using both RE and FE prior to conducting the NMA, to evaluate statistical heterogeneity of the studies. Pairwise meta-analyses were conducted to assess heterogeneity, measured through Cochran's Q, tau, and I^2 statistics (Appendix D, Section D.4). The results of these pairwise meta-analyses are presented in Appendix D (Section D.5.2). Results of the pairwise analyses were used to confirm the outputs from the NMA.

Bayesian NMAs (120, 123) were conducted for OS and PFS as described in NICE DSU TSD 2 (120). For all included studies, ITT population data were used. For OS and PFS, contrast-level data were used as inputs (i.e. log-hazards [HR] and their standard errors [SEs]), as sourced from the key clinical publications identified by the clinical SLR. Standard errors were calculated from 95% CIs using the width of the 95% interval of the log-HRs, divided by 3.92 (as 95% intervals are generated as the mean +/- 1.96*SE). The reference treatment was BSC. Both RE and FE approaches were conducted in OpenBUGS (version 3.2.3), using the BRugs package in R.

All Bayesian analyses were conducted performing Markov Chain Monte-Carlo (MCMC) simulations using three chains. After discarding the initial 50,000 simulations as burn-in samples, three sets of 50,000 simulations were used for parameter estimation. Bayesian model comparisons used deviance information criterion (DIC). Convergence was assessed

using Brooks-Gelman-Rubin diagnostic plots (124, 125), the ratio of Monte Carlo (MC) error to the standard deviation (SD), and autocorrelation. Convergence was considered achieved when the ratio was <0.05. If not, additional run-in was performed (126, 127). The median and percentiles of posterior samples estimated the effect and its 95% credible interval (CrI). These samples were also used to determine treatment ranking probabilities, fruquintinib's superiority, and the surface under the ranking curve (SUCRA) index for each treatment (128). League tables and forest plots were generated for all analyses.

Model fit was evaluated using the deviance information criterion (DIC) (136). Where marginal DIC differences were observed between the models, the model with improved convergence (MC error to SD ratio <0.05), and autocorrelation was selected. Visual inspection of density plots and trace plots was also conducted. The best fitting model was identified for each analysis and is reported in the results section (Section B.2.9.5). The full methodology of the NMA is presented in Appendix D (Section D4).

B.2.9.5 Results of the network meta-analysis

For both OS and PFS, the Bayesian FE models were used for the base case analysis based on the assessment of heterogeneity and model fit. OS and PFS model fit assessments (RE and FE) are presented in Appendix D (Section D.5.1.1 and Section D.5.1.2, respectively).

For OS, the DIC for the FE model was -5.58 with a mean residual deviance of 8.6, compared to -5.58 and 7.5 for the RE model, respectively. For PFS, the DIC for the FE model was -1.46 with a mean residual deviance of 13.0, compared to -3.05 and 8.3 for the RE model, respectively. For both OS and PFS, the residual deviance was close to the number of data points (n=8) in each analysis. The ratio of MC error to the SD was <0.05 (0.01) in both RE and FE models, and visual inspection of density plots and trace plots suggested convergence of the models.

A random effects analysis is presented in Appendix D. However, as there are fewer than five studies per treatment comparison, there is likely to be insufficient information to reliably estimate the between study heterogeneity in the RE model (125) also suggesting the FE model results may be more reliable. This is consistent with the company base case NMA in TA866 (7), although it is unclear whether the fixed or random effects model informed the committee’s preferred base case.

B.2.9.5.1 Overall survival

All eight RCTs were included in the base case NMA for OS; input data are provided in Table 18).

Table 18: Base case NMA, OS input data

Study	Treatment†	Comparator	OS HR	OS SE, log HR	n
Xu, 2017b	Fruquintinib	BSC‡	0.71	0.32	71
FRESCO-2	Fruquintinib	BSC‡	0.66	0.10	691
FRESCO	Fruquintinib	BSC‡	0.65	0.12	416
CORRECT	Regorafenib	BSC‡	0.77	0.10	760
CONCUR	Regorafenib	BSC‡	0.55	0.17	204
RECOURSE	Trifluridine-tipiracil	BSC‡	0.68	0.09	800
TERRA	Trifluridine-tipiracil	BSC‡	0.79	0.12	406
Yoshino, 2012	Trifluridine-tipiracil	BSC‡	0.56	0.19	169

†Treatments were in combination with BSC. ‡BSC was in combination with placebo
Abbreviations: BSC, best supportive care; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; SE, standard error.

Fruquintinib was associated with a significant reduction in the risk of death vs BSC (HR: 0.66 [95% CrI: 0.57, 0.76]) (Table 19 and Figure 18). This is consistent with the results observed in the FRESCO (HR: 0.65 [95% CI: 0.51, 0.83]; p<0.001) and FRESCO-2 (HR: 0.66 [95% CI: 0.55, 0.80]; p<0.001) RCTs and the results estimated by the pairwise meta-analysis of FRESCO and FRESCO-2 (fixed effects HR: 0.66 [95% CI: 0.57, 0.76] and random effects HR: 0.66 [95% CI: 0.57, 0.76]; Section B.2.8).

Regorafenib and trifluridine-tipiracil were also associated with a significant reduction in the risk of death vs BSC (HR: 0.71 [95% CrI: 0.60, 0.83] and HR: 0.69 [95% CrI: 0.61, 0.79], respectively). These results are consistent with the observed HRs reported in individual included RCTs (Table 23) and estimated HRs from the FE NMA presented in TA866 (HR: 0.68 [95% CrI: 0.59, 0.78] and HR: 0.68 [95% CrI: 0.62, 0.76] for regorafenib vs BSC and trifluridine-tipiracil vs BSC, respectively).

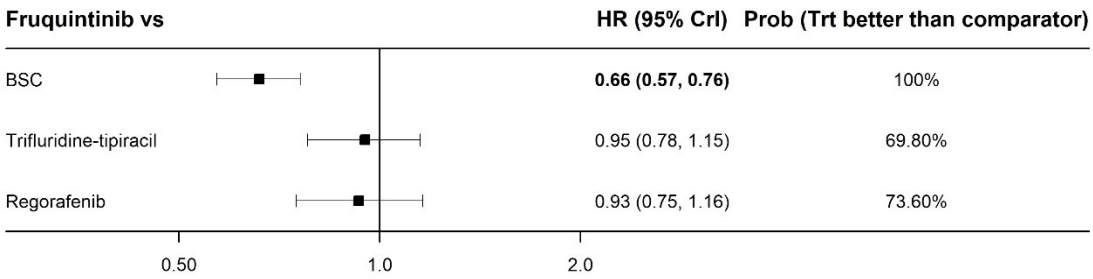
Results from the NMA indicate a numerical advantage in the reduction of the risk of death for fruquintinib vs trifluridine-tipiracil (HR: 0.95 [95% CrI: 0.78, 1.15]), and vs regorafenib (HR: 0.93 [95% CrI: 0.75, 1.16]) (Table 19 and Figure 18), however this is not statistically significant. This results in fruquintinib being ranked first in the network among all treatments (Figure 19), with a SUCRA value of 81%. Additionally, the probability that fruquintinib was better than regorafenib and trifluridine-tipiracil was 62% and 56%, respectively (Figure 19). The ranking results were consistent with the NMA.

Table 19: Base case: OS, league tables fixed effects NMA: HR (95% CrI)

BSC‡			
0.69 [0.61, 0.79]	**Trifluridine-tipiracil†**		
0.71 [0.60, 0.83]	1.02 [0.83, 1.26]	**Regorafenib†**	
0.66 [0.57, 0.76]	0.95 [0.78, 1.15]	0.93 [0.75, 1.16]	**Fruquintinib†**

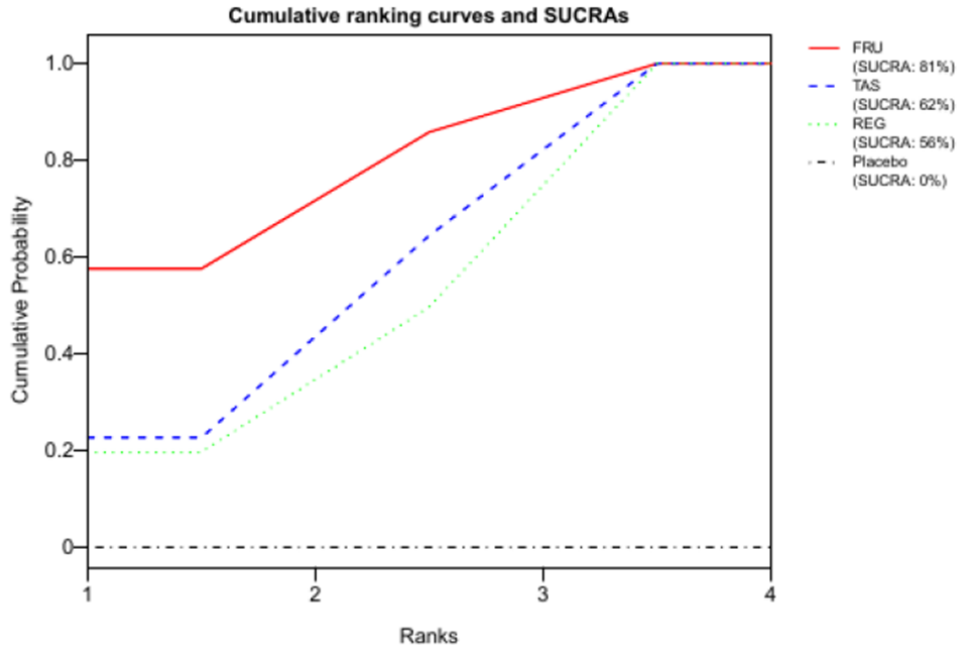
The estimates are for interventions in rows vs comparators in columns. Results are HR [95% CrI].
†Treatments were in combination with BSC. ‡BSC was in combination with placebo.
Abbreviations: BSC, best supportive care; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival.

Figure 18: Base case: OS, fixed effects NMA: HR (95% CrI): Fruquintinib vs BSC, trifluridine-tipiracil, and regorafenib



Treatments were in combination with BSC. BSC was in combination with placebo
Abbreviations: BSC, best supportive care; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; prob, probability; trt, treatment.

Figure 19: Cumulative ranking curve and SUCRA plot (fixed effects) for all treatments for OS



Abbreviations: FRU, fruquintinib; OS, overall survival; REG, regorafenib; SUCRA, Surface Under the Cumulative Ranking Curves; TAS, trifluridine-tipiracil.

B.2.9.5.2 Progression-free survival

All eight RCTs were included in the base case NMA for PFS; input data are provided in (Table 20).

Table 20: Base case NMA, PFS input data

Study	Treatment†	Comparator‡	PFS HR	PFS SE, log HR	n
Xu, 2017b	Fruquintinib	BSC	0.30	0.35	71
FRESCO-2	Fruquintinib	BSC	0.32	0.09	691
FRESCO	Fruquintinib	BSC	0.26	0.12	416
CORRECT	Regorafenib	BSC	0.49	0.08	760
CONCUR	Regorafenib	BSC	0.31	0.18	204
RECOURSE	Trifluridine-tipiracil	BSC	0.48	0.08	800
TERRA	Trifluridine-tipiracil	BSC	0.43	0.12	391
Yoshino, 2012	Trifluridine-tipiracil	BSC	0.35	0.18	169

†Treatments were in combination with BSC. ‡BSC was in combination with placebo
Abbreviations: BSC, best supportive care; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; SE, standard error.

Fruquintinib was associated with a significant reduction in the risk of progression or death vs BSC (HR: 0.30 [95% CrI: 0.26, 0.34]) (Table 21 and Figure 20). This is consistent with the results observed in FRESCO (HR: 0.26 [95% CI: 0.21, 0.34]; p<0.001) and FRESCO-2 (HR: 0.32 [95% CI: 0.27, 0.39]; p<0.001), and the results estimated by the pairwise meta-analysis of FRESCO and FRESCO-2 (FE HR: 0.30 [95% CI: 0.26, 0.34], RE HR: 0.29 [95% CI: 0.24, 0.36]) (Section B.2.8).

Regorafenib and trifluridine-tipiracil were also associated with a significant reduction in the risk of progression or death vs BSC (HR: 0.45 [95% CrI: 0.39, 0.52] and HR: 0.44 [95% CrI: 0.39, 0.50], respectively). These results are consistent with the observed HRs reported in the individual included RCTs (Table 20) and estimated HRs from the FE NMA presented in TA866 (HR: 0.42 [95% CrI: 0.39, 0.45] and HR: 0.45 [95% CrI: 0.42, 0.48] for regorafenib vs BSC and trifluridine-tipiracil vs BSC, respectively).

Results from the NMA indicate that fruquintinib was associated with a significant reduction in the risk of progression or death vs trifluridine-tipiracil (HR: 0.67 [95% CrI: 0.55, 0.80]), and vs regorafenib (HR: 0.66 [95% CrI: 0.54, 0.81]) (Table 21 and Figure 20). Fruquintinib was ranked first in the network with a SUCRA value of 100%. Additionally, the probability that

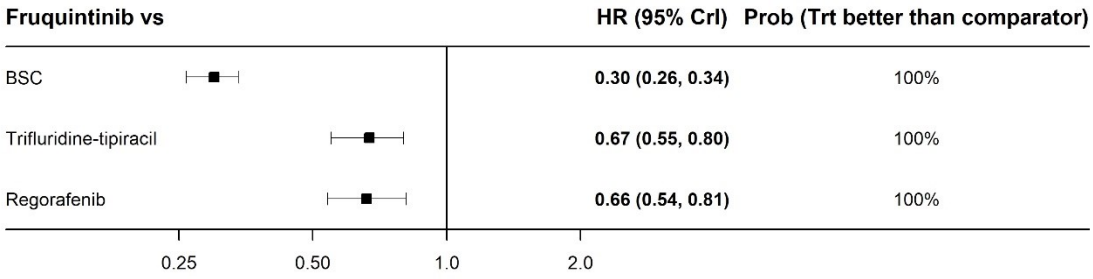
fruquintinib was better than trifluridine-tipiracil and regorafenib was both 100% (Figure 21). The ranking results were consistent with the NMA.

Table 21: Base case: PFS, league tables fixed effects NMA: HR (95% CrI)

BSC‡			
0.45 [0.39, 0.50]	**Trifluridine tipiracil†**		
0.45 [0.39, 0.52]	1.01 [0.84, 1.23]	**Regorafenib†**	
0.30 [0.26, 0.34]	0.67 [0.55, 0.80]	0.66 [0.54, 0.81]	**Fruquintinib†**

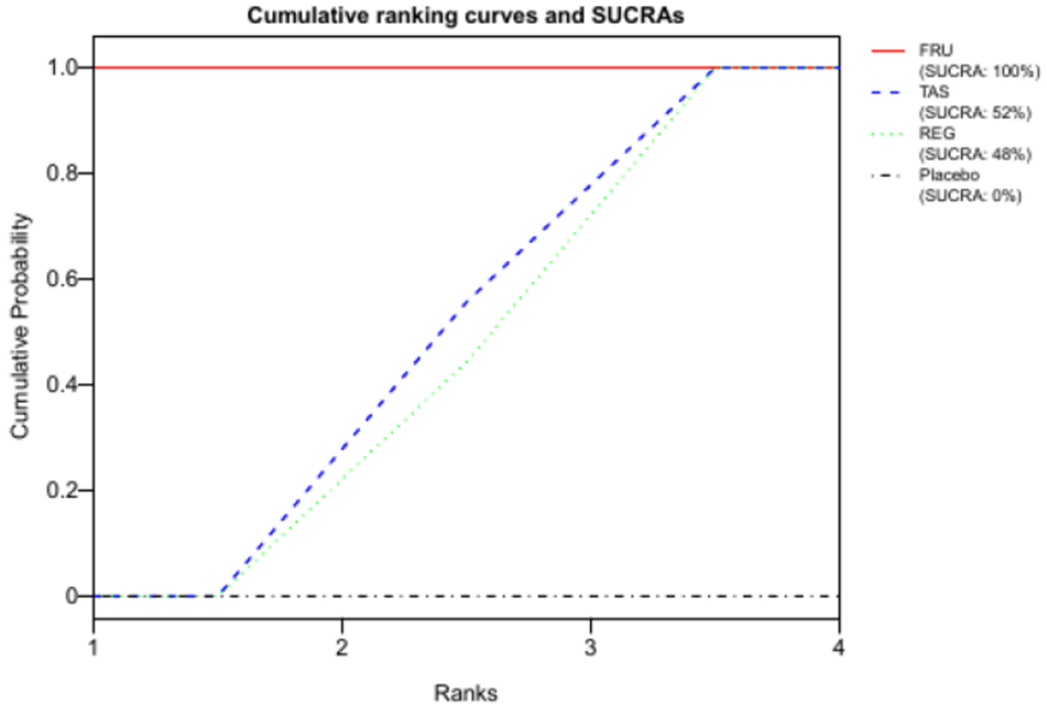
The estimates are for interventions in rows vs comparators in columns. Results are HR [95% CrI].
†Treatments were in combination with BSC. ‡BSC was in combination with placebo
Abbreviations: BSC, best supportive care; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival.

Figure 20: Base case: PFS, fixed effects NMA: HR (95% CrI): Fruquintinib vs BSC, trifluridine-tipiracil, and regorafenib



Treatments were in combination with BSC. BSC was in combination with placebo
Abbreviations: BSC, best supportive care; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; PFS, progression free survival; prob, probability; trt, treatment.

Figure 21: Cumulative ranking curve and SUCRA plot (fixed effects) for all treatments for PFS



Treatments were in combination with BSC. BSC was in combination with placebo
Abbreviations: FRU, fruquintinib; PFS, progression-free survival; REG, regorafenib; SUCRA, Surface Under the Cumulative Ranking Curves; TAS, trifluridine-tipiracil.

B.2.9.6 Scenario analyses

A series of scenario analyses were conducted to explore the impact of heterogeneity in the distribution of potential treatment effect modifiers between studies on the NMA results (Section B.2.9.5 and Appendix D [Section D.3.1.2]) (123).

As described in Section B.2.9.3, prior anti-VEGF treatment (prior anti-VEGF vs no prior anti-VEGF), ethnicity (Asian vs non-Asian), ECOG PS (ECOG 0 vs ECOG 1), liver metastases (with liver metastasis vs no liver metastasis), number of metastatic sites and number of prior lines of treatment for metastatic disease were identified as potential treatment-effect modifiers. Subgroup analyses were conducted for prior anti-VEGF treatment, ethnicity, liver metastases, and ECOG status. Subgroup analyses for number of metastatic sites and number of prior lines of treatment were not conducted due to the limited and inconsistent reporting of outcomes across trials (Appendix D, Section D.3.1.2): data for number of metastatic sites were available in seven RCTs but were inconsistently reported i.e. grouping of data by number of metastatic sites varied across the studies, and data for number of prior lines of treatment were grouped inconsistently across the studies (Appendix D, Section D.3.1.2).

Only studies with data available for the relevant population contributed to each analysis, i.e. this involved either the full ITT population or subgroup data (Table 22). If only a subgroup of patients were relevant for the analysis, subgroup data were used to inform the scenario.

Table 22: Studies contributing to the NMA subgroup-based scenario analyses

Scenario analysis	FRESCO	FRESCO-2	Xu, 2017	CONCUR	CORRECT	Yoshino, 2012	RECOURSE	TERRA
Prior anti-VEGF	X	X	X†	X	X	X		
No prior anti-VEGF	X	X‡	X†	X		X		
With liver metastasis	X	X	X†			X		
No liver metastasis	X	X	X†			X		
Asian	X	X	X	X	X	X	X	X
Non-Asian		X			X		X	
ECOG 0	X	X		X	X	X	X	X‡
ECOG 1	X	X	X†	X	X	X	X	X‡

X indicates inclusion in the analysis.
†Included for PFS analyses only due to data availability; ‡Included for OS analyses only due to data availability.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NMA, network meta-analysis; VEGF, vascular endothelial growth factor.

Data inputs for OS and PFS NMAs for subgroup analyses are presented in Appendix D. Results for OS and PFS from these subgroup analyses for the fruquintinib vs BSC, fruquintinib vs regorafenib, and fruquintinib vs trifluridine-tipiracil comparisons are summarised in Section B.2.9.6.1, Section B.2.9.6.2, and Section B.2.9.6.3, respectively. For consistency between the base case and scenario analysis outputs, all analyses presented are based on fixed-effects models. Scenario analyses results, including league tables and outcomes for random effects models, are provided in Appendix D (Section D.5.4). Overall, results across scenarios, for both OS and PFS, were broadly consistent with the base case analysis, showing consistency in the direction of effect for fruquintinib vs regorafenib, trifluridine-tipiracil and BSC.

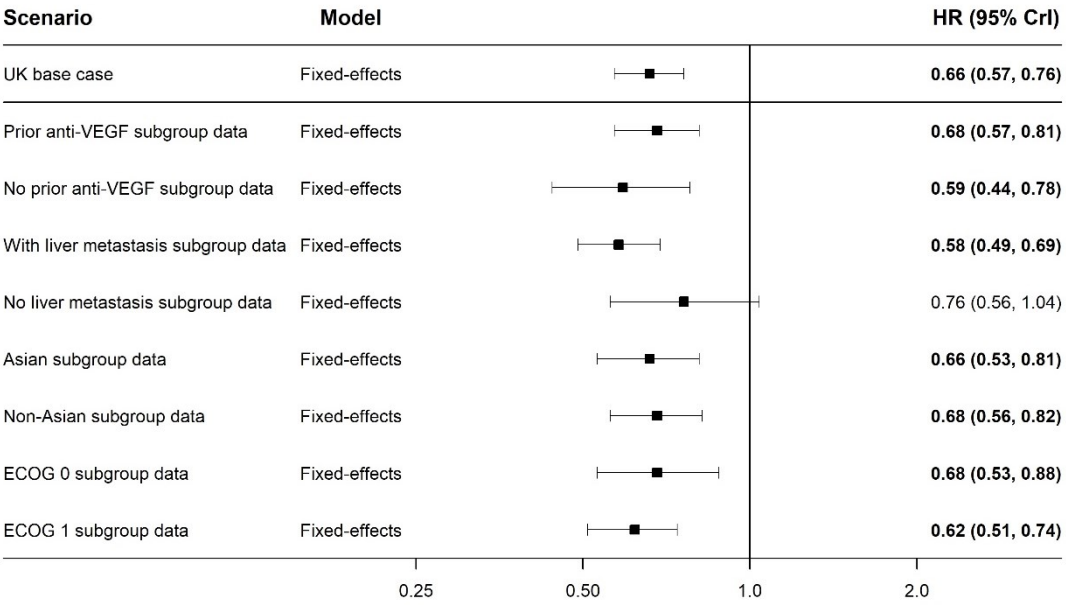
For completeness, in alignment with the approach in TA866 (7), scenario analyses based on grouping of studies were also conducted and are presented in Appendix D (Section D.5.5). However, advisors at the UK market access advisory board (1st December 2023) believed that the subgroup-based scenario analyses were more informative than scenarios based on the grouping of studies, as they were informed by a greater number of RCTs (47).

B.2.9.6.1 Fruquintinib vs BSC

Subgroup-based scenario analysis results for both OS and PFS were broadly consistent with the base case analysis, showing a significant reduction in the risk of death and the risk of progression or death for fruquintinib vs BSC in almost every scenario (Figure 22 and Figure 23 for OS and PFS, respectively). This conclusion was supported by clinical and health economic experts at a UK market access advisory board (1st December 2023) (47).

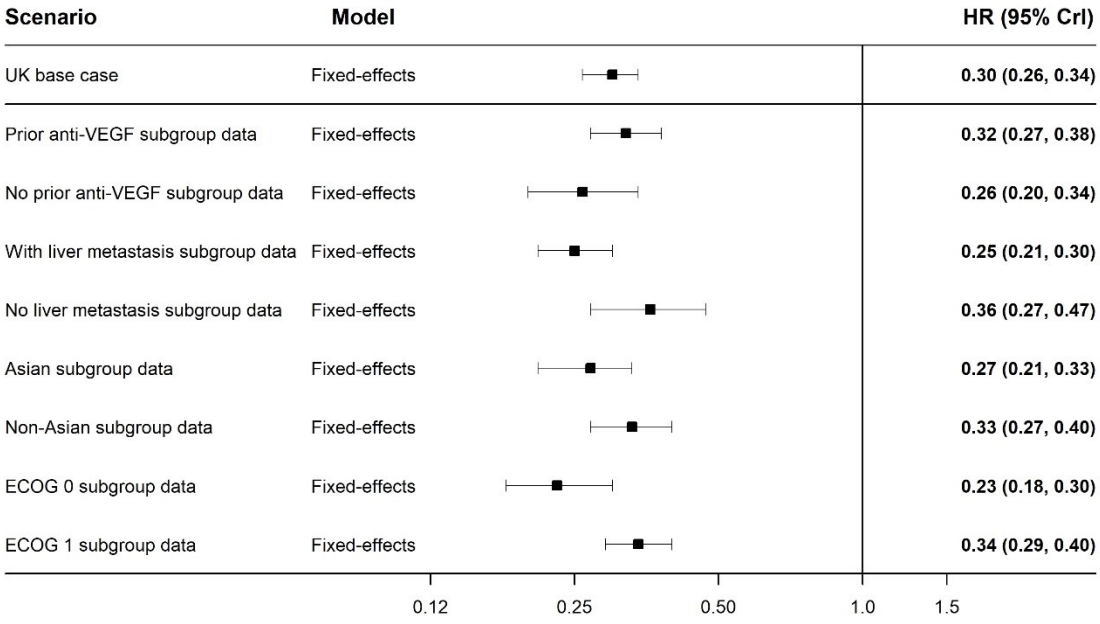
The HR estimates differed numerically vs the base case analysis, however overall conclusions were unchanged. For the subgroup analyses for OS and PFS based on prior anti-VEGF use, the effect of fruquintinib vs BSC was consistent with the base case, with a greater numerical advantage for fruquintinib in the “no prior anti-VEGF use” subgroup. For the “no liver metastases” subgroup, the credible interval crossed one for OS, likely due to the low patient numbers informing the analysis (only 31% [n/N = 129/416 of patients from FRESCO, 28% [n/N = 196/691] of patients from FRESCO-2 and 57% of [n/N = 96/169] patients from Yoshino 2012; Appendix D, Section D.5.4.1).

Figure 22: Forest plot OS fruquintinib vs BSC (fixed effects scenario analyses)



Treatments were in combination with BSC. BSC was in combination with placebo
Abbreviations: BSC, best supportive care; CrI, credible interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; UK, United Kingdom; VEGF, vascular endothelial growth factor.

Figure 23: Forest plot PFS fruquintinib vs BSC (fixed effects scenario analyses)



Treatments were in combination with BSC. BSC was in combination with placebo
Abbreviations: BSC, best supportive care; CrI, credible interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival; UK, United Kingdom; VEGF, vascular endothelial growth factor.

B.2.9.6.2 Fruquintinib vs regorafenib

For fruquintinib compared to regorafenib, subgroup-based sensitivity analysis results for both OS and PFS were broadly consistent with the base case analysis, showing consistency in

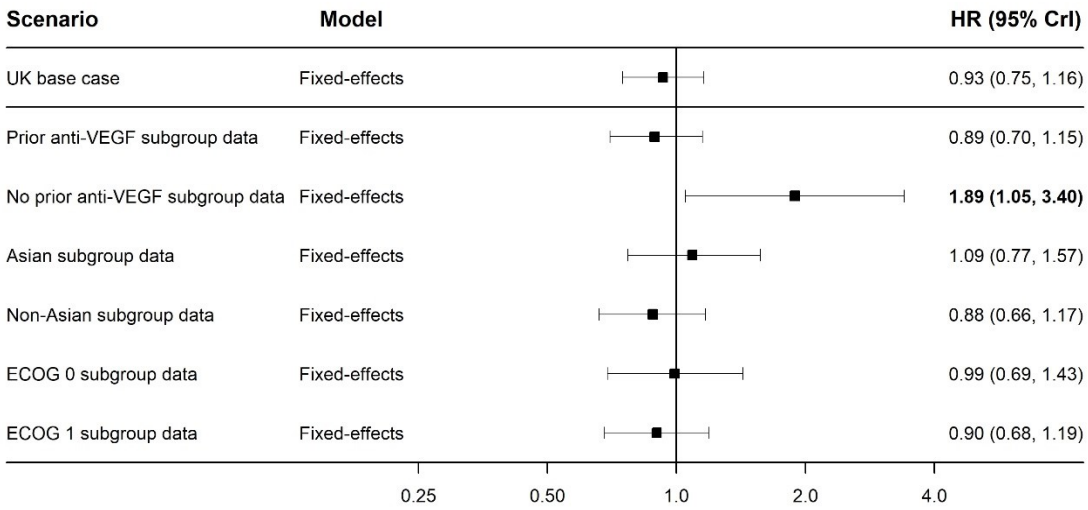
the direction of effect (Figure 24 and Figure 25). This conclusion was supported by clinical and health economic experts at the UK market access advisory board (1st December 2023) conducted by Takeda (47).

For OS, the majority of results were consistent with the base case. In the subgroup of patients who had no prior anti-VEGF, the direction of effect varied from the base case (HR >1), the credible intervals were wide and did not cross one. These results should be interpreted with caution as the input data for regorafenib was based on only 40% (n/N = 82/204) of patients from one RCT assessing regorafenib vs BSC (CONCUR) (Appendix D, Section D.5.4.1). In the Asian subgroup, the direction of effect varied from the base case (HR >1), but the credible interval crossed one. The results of all other scenarios were aligned with the base case in terms of direction of effect.

For PFS, in all but two scenarios, fruquintinib was associated with a significant reduction in the risk of progression or death vs regorafenib. In the Asian subgroup, the PFS HR was comparable to the base case analysis in terms of direction of effect, but the credible interval crossed one. Similar to OS, the direction of effect in the subgroup of patients who had no prior anti-VEGF varied from the base case (HR >1), the credible interval was wide and crossed one. Similarly, these results should be interpreted with caution as the analysis was informed by only 40% (n/N = 82/204) of patients from one study assessing regorafenib vs BSC (CONCUR) (Appendix D, Section D.5.4.1).

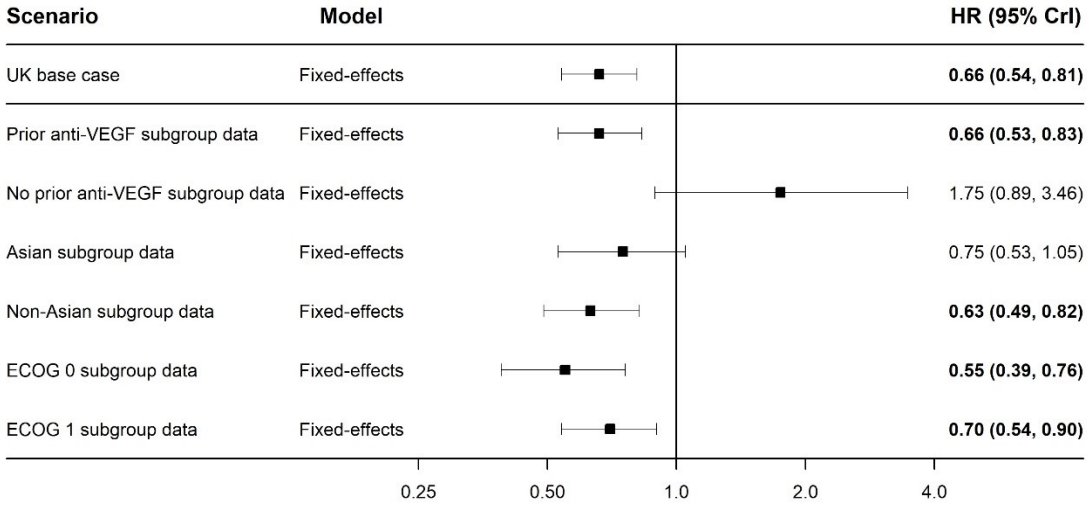
It was not possible to conduct subgroup-based sensitivity analysis for either OS or PFS for the subgroup with liver metastases due to the lack of available data reported in the regorafenib RCTs.

Figure 24: Forest plot OS fruquintinib vs regorafenib (fixed effects scenario analyses)



Treatments were in combination with BSC. BSC was in combination with placebo
Abbreviations: CrI, credible interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; UK, United Kingdom; VEGF, vascular endothelial growth factor.

Figure 25: Forest plot PFS fruquintinib vs regorafenib (fixed effects scenario analyses)



Treatments were in combination with BSC. BSC was in combination with placebo
Abbreviations: CrI, credible interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival; UK, United Kingdom; VEGF, vascular endothelial growth factor.

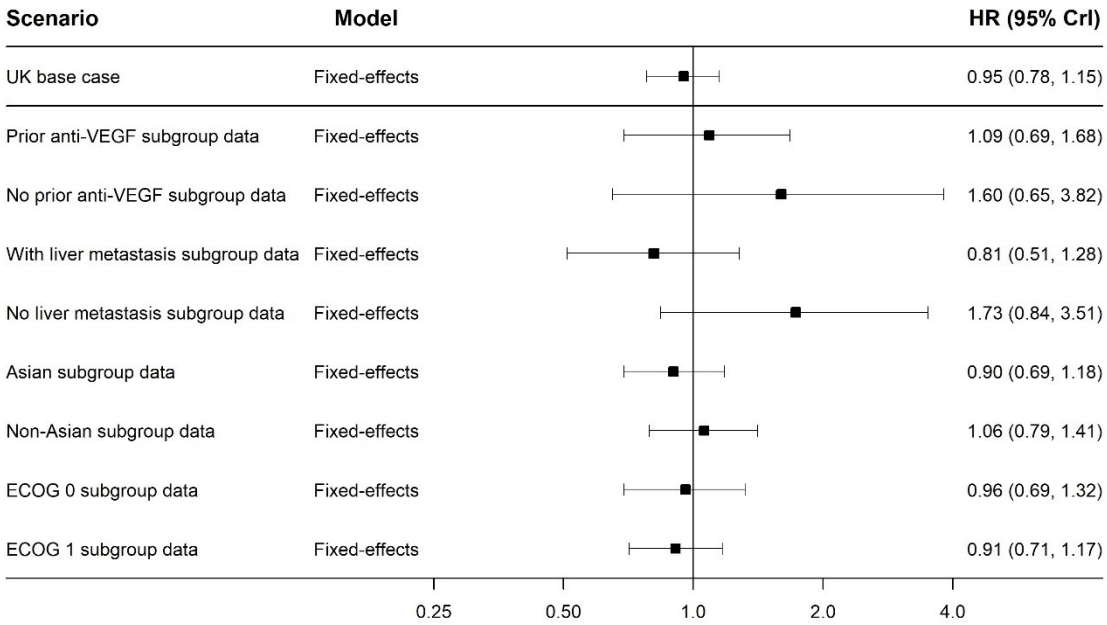
B.2.9.6.3 Fruquintinib vs trifluridine-tipiracil

Compared with trifluridine-tipiracil, subgroup-based sensitivity analysis results for OS and PFS were broadly consistent with the base case analysis (Figure 26 and Figure 27). This conclusion was supported by clinical and health economic experts at the UK market access advisory board (1st December 2023) (47).

All OS scenario results were aligned with the base case analysis. In four of the subgroup analyses (prior anti-VEGF, no prior anti-VEGF, no liver metastases, and non-Asian subgroups) the direction of effect varied from the base case (HR >1), but the 95% CrIs still crossed one. Wide credible intervals in these analyses also indicate uncertainty in results, likely due to the reduction in patient numbers contributing to the analysis for trifluridine-tipiracil. For example, for the prior anti-VEGF, no prior anti-VEGF and no liver metastases scenarios, only 79% (n/N = 134/169), 21% (n/N = 35/169 and 39% (66/169) of patients from one RCT assessing trifluridine-tipiracil vs BSC (Yoshino, 2012) contributed to the analyses, respectively (Appendix D, Section D.5.4.1).

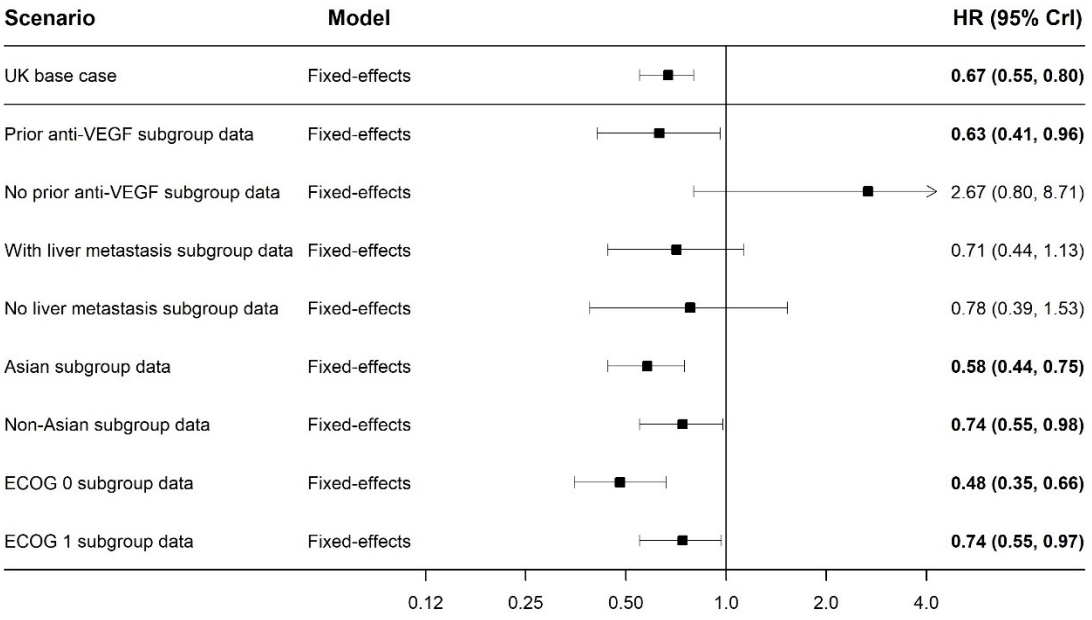
For PFS, in five out of eight scenarios conducted, fruquintinib was associated with a significant reduction in the risk of progression or death vs trifluridine-tipiracil. In the liver metastases subgroup analyses, the PFS HRs were comparable to the base case analysis in terms of direction of effect, but the credible intervals crossed one. The wide confidence intervals in these scenarios are likely due to the reduction in patient numbers contributing to the analysis (n/N=103/169 [61%] for the liver metastasis subgroup; n/N=66/169 [39%] for the no liver metastasis subgroup). Only the no prior anti-VEGF subgroup, differed to the base case analysis in terms of direction of effect, with a wide credible interval crossing one. This result should be interpreted with caution as the analysis was informed by only 21% (n/N=35/169) of patients (Appendix D, Section D.5.4.1).

Figure 26: Forest plot OS fruquintinib vs trifluridine-tipiracil (fixed effects scenario analyses)



Treatments were in combination with BSC. BSC was in combination with placebo
Abbreviations: CrI, credible interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; UK, United Kingdom; VEGF, vascular endothelial growth factor.

Figure 27: Forest plot PFS fruquintinib vs trifluridine-tipiracil (fixed effects scenario analyses)



Treatments were in combination with BSC. BSC was in combination with placebo
Abbreviations: CrI, credible interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival; UK, United Kingdom; VEGF, vascular endothelial growth factor.

B.2.9.7 Uncertainties in the indirect and mixed treatment comparisons

The NMAs generated relative effects for fruquintinib vs regorafenib, trifluridine-tipiracil and BSC, as per the NICE scope. The NMA was informed by all available RCT evidence identified by the SLR for these comparators, all of which were deemed to have a low risk of bias based on the Cochrane Risk of Bias (RoB) tool. Moreover, the NMA followed methodological guidance based on TSD 2 (120) and TSD 3 (123).

All RCTs assessed for inclusion in the NMA were considered comparable with respect to study design and inclusion/exclusion criteria, treatment dosing, and endpoint definitions. Experts at the UK market access advisory board (1st December 2023) considered any differences minor and not of concern: despite some variation in trial phases (Phase II vs Phase III), all trials were deemed appropriate for inclusion. Although differences existed in geographic location and prior therapy requirements, they were considered minor and unlikely to substantially influence results and advisors considered that there was no compelling reason to exclude any trials from the network.

As described in Section B.2.9.2, imbalances in baseline characteristics across included studies were identified with respect to ethnicity, ECOG PS, number of metastatic sites, presence of liver metastases, number of prior treatments received, and prior anti-VEGF. An assessment was conducted to explore the potential treatment effect modification due to these factors. Prior anti-VEGF treatment (prior anti-VEGF vs no prior anti-VEGF) was considered the only likely effect modifier, with other factors considered potentially or not to be effect modifiers based on limited and contradictory evidence. Despite experts at the UK market access advisory board (1st December 2023) (47) stating that it was unnecessary to adjust for treatment effect modifiers at this late line of treatment, a series of scenario analyses were conducted to evaluate uncertainty in the base case analysis based on subgroup data (Section B.2.7) and groupings of trials (Appendix D). These scenarios yielded highly consistent results vs the base case analyses, which further supported the robustness of the base case results and demonstrated that heterogeneity in baseline patient characteristics and potential effect modifiers between trials had minimal impact on NMA results.

Moreover, as described in Section B.2.3, trial inclusion criteria specified that patients in FRESCO-2 had to have received prior trifluridine-tipiracil and/or regorafenib, and PFS and OS benefits with fruquintinib were observed regardless of previous treatment with trifluridine-tipiracil and/or regorafenib. Notably, FRESCO-2 is the only study of those identified by the

clinical SLR and included in the NMA which mandated prior receipt of these therapies. RECOURSE is the only study to report the proportion of patients who received prior regorafenib 18% (n/N = 144/800), with the remaining included studies not specifying. Therefore, receipt of prior trifluridine-tipiracil or regorafenib could not be explored or adjusted for within the NMA and is a limitation of the analysis.

Despite the acknowledged limitations, the results of the base case NMA and supporting scenarios indicate that fruquintinib is associated with a significant reduction in the risk of progression or death vs regorafenib, trifluridine-tipiracil and BSC, and a numerical advantage in OS vs regorafenib, trifluridine-tipiracil, and BSC. Notably, based on SUCRA values, fruquintinib is ranked first in both networks for both PFS and OS. Moreover, the NMA methodology was considered appropriate and robust by advisors at the UK market access advisory board (47); highlighting the comprehensiveness of treatment effect modifier assessment and the comprehensive scenario analyses (47). The advisors commented specifically on the consistent results from the scenario analyses, and as a consensus, agreed that the NMA results uniformly supported the presence of consistent treatment effects of fruquintinib vs all treatments listed in the final scope for previously untreated mCRC (47).

B.2.10 Adverse reactions

The safety profile of fruquintinib was consistent across FRESCO and FRESCO-2, with most treatment-emergent adverse events (TEAE) treatable and manageable. In both trials, patients who received fruquintinib stayed on treatment for almost twice as long as those who received placebo. This importantly supports the favourable tolerability of fruquintinib, even in a heavily pre-treated population.

B.2.10.1 Overview of treatment-emergent adverse events

Fruquintinib was generally well tolerated. The majority of TEAEs and serious TEAEs/ adverse events of special interest (AESI) were managed with supportive care and established monitoring and treatment guidelines, including dose adjustments. An overall summary of safety findings for FRESCO and FRESCO-2 is presented in Appendix F.

FRESCO: The median treatment exposure was twice as long for fruquintinib (3.7 months; range: 0.1–21.9 months) as it was for placebo (1.8 months; range: 0.1–11.1 months), with mean RDIs of 92.0% and 98.0% in the fruquintinib and placebo arms, respectively.

In the fruquintinib arm, 98.6% of patients experienced any TEAE (vs 88.3% in the placebo arm), with Grade ≥3 TEAEs occurring in 61.2% of patients (vs 19.7% in the placebo arm). In the fruquintinib arm, the incidence of TEAEs leading to dose reduction and treatment interruption was 24.1% and 35.3%, respectively (placebo arm: 4.4% and 10.2%, respectively); 15.1% of patients experienced a TEAE that led to treatment discontinuation (placebo arm: 5.8%), with 15.5% experiencing 1 serious TEAE (placebo arm: 5.8%). In the fruquintinib arm, 3.2% of patients were reported to have TEAEs leading to death, vs 1.5% of patients in the placebo arm. In the fruquintinib arm, 92.4% of patients experienced at least one AESI, vs 54.0% in the placebo arm. Although the incidence of TEAEs was higher with fruquintinib than placebo, most occurred during the first two cycles of treatment and could be managed with supportive care and dose adjustment. Furthermore, the duration of fruquintinib treatment was twice as long as that of placebo, hence the TEAE observation periods differed between the two treatment groups, which may have contributed to the relatively higher incidence of TEAEs observed with fruquintinib (83).

FRESCO-2: The median treatment exposure was 3.1 months (range: 0.3–19.1) for fruquintinib and 1.8 months (range: 0.3–12.0) for placebo, with RDIs of 85.0% and 89.3% in the fruquintinib and placebo arms, respectively. In the fruquintinib arm, 98.9% patients experienced any TEAE (vs 92.6% in the placebo arm), with Grade ≥3 TEAEs occurring in 62.7% of patients (vs 50.4% in the placebo arm). Although there were more Grade ≥3 TEAEs in the fruquintinib arm than the placebo arm, most TEAEs, including hypertension, and asthenia, could be managed with supportive care and dose modification (63).

In the fruquintinib arm, the incidence of TEAEs leading to dose reduction and interruption was 24.1% and 46.7%, respectively (placebo arm: 3.9% and 26.5%, respectively). Discontinuations due to TEAEs were well balanced between the fruquintinib arm (20.4%) and the placebo arm (21.3%), as was the incidence of serious TEAEs (37.5% vs 38.3%). A lower percentage of patients in the fruquintinib arm (10.7%) than in the placebo arm (19.6%) experienced TEAEs leading to death; for 5.9% and 11.7% of patients, respectively, the cause of death was reported as disease progression. In the fruquintinib arm, 80.7% of patients experienced at least one AESI, vs 53.0% in the placebo arm.

Table 23: Overall summary of TEAEs – FRESCO and FRESCO-2, safety sets

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=137**	**Fruquintinib + BSC N=456**	**Placebo + BSC N=230**
Patients with any TEAE, n (%)	**274 (98.6)**	**121 (88.3)**	**451 (98.9)**	**213 (92.6)**
CTCAE Grade ≥3	170 (61.2)	27 (19.7)	286 (62.7)	116 (50.4)
Treatment-related	266 (95.7)	97 (70.8)	395 (86.6)	130 (56.5)
Treatment-related CTCAE Grade ≥3	128 (46.0)	10 (7.3)	164 (36.0)	26 (11.3)
Leading to dose reduction	67 (24.1)	6 (4.4)	110 (24.1)	9 (3.9)
Leading to dose interruption	98 (35.3)	14 (10.2)	213 (46.7)	61 (26.5)
Leading to treatment discontinuation	42 (15.1)	8 (5.8)	93 (20.4)	49 (21.3)
Treatment-related leading to dose reduction	61 (21.9)	3 (2.2)	93 (20.4)	7 (3.0)
Treatment-related leading to dose interruption	87 (31.3)	10 (7.3)	134 (29.4)	14 (6.1)
Treatment-related leading to treatment discontinuation	22 (7.9)	1 (0.7)	45 (9.9)	7 (3.0)
Leading to death	4 (1.4)	0	48 (10.5)	45 (19.6)
Patients with any serious TEAE, n (%)	**43 (15.5)**	**8 (5.8)**	**172 (37.7)**	**88 (38.3)**
CTCAE Grade ≥3	32 (11.5)	7 (5.1)	163 (35.7)	85 (37.0)
Treatment-related	17 (6.1)	2 (1.5)	43 (9.4)	8 (3.5)
Treatment-related CTCAE Grade ≥3	128 (46.0)	10 (7.3)	38 (8.3)	6 (2.6)
Patients with any AESI, n (%)	**257 (92.4)**	**74 (54.0)**	**368 (80.7)**	**122 (53.0)**
Patients with any COVID-19-related TEAEs, n (%)	**N/A**	**N/A**	**14 (3.1)**	**8 (3.5)**
CTCAE Grade ≥3	N/A	N/A	1 (0.2)	5 (2.2)
Serious	N/A	N/A	1 (0.2)	5 (2.2)
Treatment-related	N/A	N/A	0	0
Treatment-related CTCAE Grade ≥3	N/A	N/A	0	0
Leading to dose reduction	N/A	N/A	0	0
Leading to dose interruption	N/A	N/A	6 (1.3)	4 (1.7)
Leading to treatment discontinuation	N/A	N/A	0	1 (0.4)

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=137**	**Fruquintinib + BSC N=456**	**Placebo + BSC N=230**
Treatment-related leading to dose reduction	N/A	N/A	0	0
Treatment-related leading to dose interruption	N/A	N/A	0	0
Treatment-related leading to treatment discontinuation	N/A	N/A	0	0
Leading to death	N/A	N/A	0	1 (0.4)

Source: FRESCO final CSR (86), FRESCO-2 final CSR (93).
Abbreviations: AESI, adverse event of special interest; BSC, best supportive care; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; N/A, not applicable; TEAE, treatment-emergent adverse event.

B.2.10.2 Most frequently reported TEAEs

TEAEs that occurred in ≥10% of all patients in either FRESCO or FRESCO-2 are presented by PT and Common Terminology Criteria for Adverse Events (CTCAE) Grade in Table 24. Hypertension and hand-foot syndrome are two of the most frequent toxicities associated with fruquintinib and the VEGFR class of agents. Clinical experts at the UK oncologist advisory board (22nd September 2023) stated that hypertension is not a TEAE of concern, and it is often treated in the primary care setting (11). For patients with a baseline history of hypertension or hypertension that developed on the study, blood pressure was monitored as per institutional standard practice. Most patients with hand-foot syndrome were treated with topical ointment (urea cream or burn pain relief ointment), and the symptoms were alleviated or relieved.

FRESCO: The most reported TEAEs of any grade by preferred term (PT) in the fruquintinib arm were hypertension (57.2%), hand-foot syndrome (49.3%) and proteinuria (43.2%). The most reported TEAEs of any grade by PT in the placebo arm were proteinuria (24.8%), elevated aspartate aminotransferase (17.5%) and hypertension (15.3%).

FRESCO-2: The most frequently reported TEAEs of any grade in the fruquintinib arm were hypertension (36.8%), asthenia (34.0%) and decreased appetite (27.2%); in the placebo arm, the most frequently reported TEAEs of any grade were asthenia (22.6%), nausea (18.3%) and decreased appetite (17.4%).

Table 24: TEAEs reported in ≥10% patients by PT and grade – FRESCO and FRESCO-2, safety sets

	FRESCO				FRESCO-2			
	Fruquintinib + BSC N=278		Placebo + BSC N=137		Fruquintinib + BSC N=456		Placebo + BSC N=230	
	Grade 1–2 n (%)	Grade ≥3 n (%)	Grade 1–2 n (%)	Grade ≥3 n (%)	Grade 1–2 n (%)	Grade ≥3 n (%)	Grade 1–2 n (%)	Grade ≥3 n (%)
No. of patients who experienced at least 1 TEAE	104 (37.4)	170 (61.1)	94 (68.6)	27 (19.7)	165 (36.2)	286 (62.7)	97 (42.2)	116 (50.4)
Abdominal distension	24 (8.6)	2 (0.7)	14 (10.2)	1 (0.7)	<10%	<10%	<10%	<10%
Abdominal pain	38 (13.7)	9 (3.2)	13 (9.5)	2 (1.5)	69 (15.1)	14 (3.1)	30 (13.0)	7 (3.0)
Anaemia	32 (11.5)	2 (0.7)	15 (10.9)	3 (2.2)	<10%	<10%	<10%	<10%
Arthralgia	<10%	<10%	<10%	<10%	46 (10.1)	4 (0.9)	10 (4.3)	0
Asthenia	33 (11.9)	2 (0.7)	3 (2.2)	0	120 (26.3)	35 (7.7)	43 (18.7)	9 (3.9)
Back pain	37 (13.3)	5 (1.8)	8 (5.8)	0	41 (9.0)	6 (1.3)	14 (6.1)	3 (1.3)
Constipation	42 (15.1)	0	11 (8.0)	2 (1.5)	76 (16.7)	2 (0.4)	22 (9.6)	0
Cough	41 (14.7)	0	15 (10.9)	0	37 (8.1)	1 (0.2)	20 (8.7)	1 (0.4)
Diarrhoea	60 (21.6)	9 (3.2)	7 (5.1)	0	94 (20.6)	16 (3.5)	24 (10.4)	0
Dysphonia	105 (37.8)	0	2 (1.5)	0	74 (16.2)	0	12 (5.2)	0
Elevated/increased ALT	60 (21.6)	2 (0.7)	13 (9.5)	2 (1.5)	33 (7.2)	14 (3.1)	8 (3.5)	1 (0.4)
Elevated ALP	28 (10.1)	3 (1.1)	12 (8.8)	1 (0.7)	<10%	<10%	<10%	<10%
Elevated/increased AST	73 (26.3)	3 (1.1)	22 (16.1)	2 (1.5)	38 (8.3)	10 (2.2)	8 (3.5)	3 (1.3)
Elevated LDH	27 (9.7)	1 (0.4)	6 (4.4)	0	<10%	<10%	<10%	<10%
Elevated total bilirubin	63 (22.7)	7 (2.5)	13 (9.5)	7 (5.1)	<10%	<10%	<10%	<10%
Fatigue	34 (12.2)	5 (1.8)	13 (9.5)	2 (1.5)	73 (16.1)	18 (3.9)	35 (15.2)	2 (0.9)
Fever/pyrexia	30 (10.8)	1 (0.4)	9 (6.6)	0	44 (9.7)	2 (0.4)	23 (10.0)	0
Hand-foot syndrome	107 (38.5)	30 (10.8)	4 (2.9)	0	59 (12.9)	29 (6.4)	6 (2.6)	0
Hypertension	99 (35.6)	60 (21.6)	18 (13.1)	3 (2.2)	106 (23.2)	62 (13.6)	18 (7.8)	2 (0.9)
Hypothyroidism	46 (16.5)	0	3 (2.2)	0	92 (20.2)	2 (0.4)	1 (0.4)	0
Increased TSH	71 (25.5)	0	3 (2.2)	0	<10%	<10%	<10%	<10%
Leukopenia	29 (10.4)	0	3 (2.2)	1 (0.7)	<10%	<10%	<10%	<10%
Loss of/decreased appetite	63 (22.7)	6 (2.2)	18 (13.1)	1 (0.7)	113 (24.8)	11 (2.4)	37 (16.1)	3 (1.3)

	FRESCO				FRESCO-2			
	Fruquintinib + BSC N=278		Placebo + BSC N=137		Fruquintinib + BSC N=456		Placebo + BSC N=230	
	Grade 1–2 n (%)	Grade ≥3 n (%)	Grade 1–2 n (%)	Grade ≥3 n (%)	Grade 1–2 n (%)	Grade ≥3 n (%)	Grade 1–2 n (%)	Grade ≥3 n (%)
Mucosal inflammation	NR	NR	NR	NR	60 (13.2)	2 (0.4)	6 (2.6)	0
Nausea	<10%	<10%	<10%	<10%	76 (16.6)	3 (0.7)	40 (17.4)	2 (0.9)
Positive faecal occult blood	46 (16.5)	0	11 (8.0)	0	NR	NR	NR	NR
Positive urine protein	29 (10.4)	3 (1.1)	6 (4.4)	0	<10%	<10%	<10%	<10%
Proteinuria	111 (39.9)	9 (3.2)	34 (24.8)	0	71 (15.5)	8 (1.8)	10 (4.3)	2 (0.9)
Stomatitis	46 (16.5)	1 (0.4)	0	0	59 (13.0)	8 (1.8)	7 (3.1)	1 (0.4)
Thrombocytopenia	32 (11.5)	8 (2.9)	3 (2.2)	0	<10%	<10%	<10%	<10%
Upper abdominal pain	36 (12.9)	1 (0.4)	11 (8.0)	0	<10%	<10%	<10%	<10%
Vomiting	<10%	<10%	<10%	<10%	59 (13.0)	7 (1.5)	24 (10.5)	4 (1.7)
Weakness	33 (11.9)	2 (0.7)	3 (2.2)	0	<10%	<10%	<10%	<10%
Weight loss/decrease	55 (19.8)	4 (1.4)	12 (8.8)	0	53 (11.5)	3 (0.7)	20 (8.7)	1 (0.4)

Source: FRESCO final CSR (86), FRESCO-2 final CSR (93).
<10% is included when rates are <10% across all columns for FRESCO or FRESCO i.e. for both Grade 1–2 and Grade ≥3 and both treatment arms.
Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BSC, best supportive care; CSR, clinical study report; LDH, lactate dehydrogenase; NR, not reported; PT, preferred term; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone.

B.2.10.3 Serious TEAEs

An overview of serious TEAEs that occurred in ≥ 1% of patients in the fruquintinib arm in FRESCO and FRESCO-2 are presented in Appendix F.

FRESCO: In the fruquintinib arm, 15.5% of patients experienced at least 1 serious TEAE, vs 5.8% in the placebo arm. In total, 11.5% of patients in the fruquintinib arm experienced at least 1 Grade ≥3 serious TEAE, vs 5.1% in the placebo arm.

FRESCO-2: The percentages of patients with serious TEAEs in the fruquintinib and placebo arms were balanced (37.7% vs 38.3%, respectively). The percentages of patients in the fruquintinib and placebo arms with at least 1 Grade ≥3 serious TEAE were also balanced (35.7% vs 37.0%, respectively).

B.2.10.4 Adverse events of special interest

Known characteristic toxic reactions to VEGFR inhibitors include liver dysfunction, haemorrhage, hypertension, proteinuria, dermatological toxicity, thyroid dysfunction, gastrointestinal perforation, infections, left ventricular ejection fraction (LVEF) decreased, myocardial ischemia/infarction and embolic and thrombotic events. An overview of AESIs in FRESCO and FRESCO-2 is presented in Table 25.

FRESCO: A total of 257 patients (92.4%) in the fruquintinib arm and 74 patients (54.0%) in the placebo arm had a treatment-emergent AESI. The incidence of Grade ≥3 AESIs was 43.9% in the fruquintinib arm vs 12.4% in the placebo arm, although it must be noted that the rate in the fruquintinib arm was driven by hypertension (23.4%). As previously described, clinicians do not regard hypertension as a TEAE of concern, and are used to treating it in the primary care setting (11).

FRESCO-2: A total of 368 patients (80.7%) in the fruquintinib arm and 122 patients (53.0%) in the placebo arm had a treatment-emergent AESI. The incidence of Grade ≥3 AESIs was 37.1% in the fruquintinib arm vs 19.1% in the placebo arm.

Table 25: Treatment-emergent AESIs by AESI Category – FRESCO and FRESCO-2, safety sets

	FRESCO				FRESCO-2			
	Fruquintinib + BSC N=278		Placebo + BSC N=137		Fruquintinib + BSC N=456		Placebo + BSC N=230	
	Grade 1–2 n (%)	Grade ≥3 n (%)	Grade 1–2 n (%)	Grade ≥3 n (%)	Grade 1–2 n (%)	Grade ≥3 n (%)	Grade 1–2 n (%)	Grade ≥3 n (%)
Patients with any AESI	**135 (48.5)**	**122 (43.9)**	**57 (41.6)**	**17 (12.4)**	**199 (43.6)**	**169 (37.1)**	**78 (33.9)**	**44 (19.1)**
Dermatological toxicity	124 (44.6)	31 (11.2)	8 (5.9)	0	126 (27.6)	31 (6.8)	26 (11.3)	1 (0.4)
Embolic and thrombotic events	2 (0.7)	0	0	1 (0.7)	7 (1.5)	14 (3.1)	10 (4.3)	2 (0.9)
Gastrointestinal perforation	1 (0.4)	5 (1.8)	0	1 (0.7)	6 (1.3)	10 (2.2)	1 (0.4)	1 (0.4)
Haemorrhage	118 (42.5)	3 (1.1)	30 (21.9)	0	57 (12.5)	8 (1.8)	18 (7.8)	4 (1.7)
Hepatic function abnormal	–	–	–	–	75 (16.5)	38 (8.3)	23 (10.0)	21 (9.1)
Hypertension	105 (37.8)	65 (23.4)	20 (14.5)	3 (2.2)	111 (24.4)	64 (14.0)	18 (7.8)	2 (0.9)
Infections	–	–	–	–	66 (14.5)	30 (6.6)	16 (6.9)	13 (5.7)
Liver injury	8 (2.9)	1 (0.4)	1 (0.7)	1 (0.7)	–	–	–	–
LVEF decreased	–	–	–	–	1 (0.2)	4 (0.9)	4 (1.7)	2 (0.9)
Myocardial ischaemia/infarction	7 (2.5)	0	1 (0.7)	0	–	–	–	–
Proteinuria	137 (49.3)	12 (4.3)	39 (28.5)	0	72 (15.7)	8 (1.8)	10 (4.3)	2 (0.9)
Thyroid dysfunction	57 (20.5)	0	8 (5.8)	0	121 (26.4)	2 (0.4)	4 (1.7)	0

Source: FRESCO final CSR (86), FRESCO-2 final CSR (93).
A dash (–) is included when AE was not reported under AESIs as per the definition for the trial of interest.
Abbreviations: AESI, adverse event of special interest; BSC, best supportive care; CSR, clinical study report; LVEF, left ventricular ejection fraction.

B.2.10.5 TEAEs related to study drug

In FRESCO and FRESCO-2, TEAEs were assessed by the investigator as either “related” or “not related” to study drug. An overview of TEAEs suspected to be related to study drug is presented in Appendix F.

FRESCO: A higher percentage of patients in the fruquintinib arm than in the placebo arm experienced treatment-related TEAEs (95.7% vs 70.8%). The three most frequent treatment-related TEAES in the fruquintinib arm compared with the placebo arm were: hypertension (55.4% vs 15.3%), hand-foot syndrome (49.3% vs 2.9%) and proteinuria (42.1% vs 24.8%) (Appendix F). In the fruquintinib arm, 46.0% of patients experienced at least 1 Grade ≥3 treatment-related TEAE, vs 7.3% of patients in the placebo arm (Table 26). Grade ≥3 hypertension occurred in 21.2% of patients in the fruquintinib arm vs 2.2% in the placebo arm, and Grade ≥3 hand-foot syndrome occurred in 10.8% of patients in the fruquintinib arm, vs 0% in the placebo arm.

FRESCO-2: A higher percentage of patients in the fruquintinib arm experienced treatment-related TEAEs, compared with the placebo arm (86.6% vs 56.5%). The three most frequent treatment-related TEAEs in the fruquintinib arm compared with the placebo arm were: hypertension (28.9% vs 5.2%), asthenia (24.6% vs 14.8%) and hand-foot syndrome (18.6% vs 2.6%) (Appendix F). In the fruquintinib arm, 36.0% of patients experienced at least 1 Grade ≥3 treatment-related TEAE, vs 11.3% of patients in the placebo arm (Table 25). Grade ≥3 hypertension occurred in 10.7% of patients in the fruquintinib arm vs 0.9% in the placebo arm, and Grade ≥3 hand-foot syndrome occurred in 6.1% of patients in the fruquintinib arm, vs 0 in the placebo arm.

Table 26: Grade ≥3 treatment-related TEAEs reported in ≥2% patients by PT – FRESCO and FRESCO-2, safety sets

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=137**	**Fruquintinib + BSC N=456**	**Placebo + BSC N=230**
No. of patients who experienced at least 1 Grade ≥3 treatment-related TEAE	**128 (46.0)**	**10 (7.3)**	**164 (36.0)**	**26 (11.3)**
Grade ≥3 treatment-related TEAE, n (%)				
Asthenia	0	0	24 (5.3)	3 (1.3)
Diarrhoea	8 (2.9)	0	15 (3.3)	0
Fatigue	3 (1.1)	0	15 (3.3)	1 (0.4)
Hand-foot syndrome	30 (10.8)	0	28 (6.1)	0

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=137	Fruquintinib + BSC N=456	Placebo + BSC N=230
Hypertension	59 (21.2)	3 (2.2)	49 (10.7)	2 (0.9)
Proteinuria	9 (3.2)	0	7 (1.5)	1 (0.4)
Thrombocytopenia/ reduced platelet count	7 (2.5)	0	0	0

Source: FRESCO final CSR (86), FRESCO-2 final CSR (93).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSC, best supportive care; CSR, clinical study report; PT, preferred term; TEAE, treatment-emergent adverse event.

B.2.10.6 TEAEs leading to dose modifications

Dose modifications due to TEAEs included dose reduction, dose interruption, and treatment discontinuation. The rates of dose interruptions/reductions due to TEAEs were similar across FRESCO and FRESCO-2 , supporting a consistent safety profile across studies. A summary of all TEAEs leading to treatment discontinuation, and an overview of TEAEs leading to dose reduction and interruption are presented in Appendix F.

FRESCO: There were more discontinuations due to TEAEs in the fruquintinib arm than in the placebo arm (15.1% vs 5.8%). There were more dose suspensions or reductions due to TEAEs in the fruquintinib arm than in the placebo arm (dose suspensions: 35.3% vs 10.2%; dose reductions: 24.1% vs 4.4%).

FRESCO-2: Discontinuations due to TEAEs were balanced between the fruquintinib and placebo arms (20.4% vs 21.3%). There were more dose interruptions or reductions due to TEAEs in the fruquintinib arm than in the placebo arm (dose interruptions 46.7% vs 26.5%, dose reductions: 24.1% vs 3.9%).

B.2.11 Ongoing studies

Several trials of fruquintinib are ongoing; one ongoing study of fruquintinib as a monotherapy in previously treated mCRC is provided in Table 27. An overview of further studies of fruquintinib as a combination therapy is available in Appendix O. Notably, the two pivotal trials for fruquintinib in the indication of interest, FRESCO and FRESCO-2, have been presented in this submission, and are both reporting mature data. The study presented in Table 27 is not expected to provide any further substantial evidence.

Table 27: Ongoing study of fruquintinib monotherapy in mCRC

Study number	Study objective	Study design	Estimated completion
NCT03251378	To evaluate the safety, tolerability, and PK of fruquintinib in patients with advanced solid tumours (including mCRC)	Multicentre, open-label, dose escalation and expansion Phase I study	March 2023

Abbreviations: mCRC, metastatic colorectal cancer; PK, pharmacokinetics.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings of the evidence base

FRESCO and FRESCO-2 are both mature, Phase III RCTs, which assessed the efficacy and safety of fruquintinib vs placebo, both in addition to BSC. Both trials were comparable in study design and endpoint definitions, and reported similar relative efficacy and safety data for fruquintinib vs placebo. In addition, both trials complement each other well and comprise a population that is considered representative of the UK patient population.

Data from both trials demonstrated a significant improvement in PFS and OS with fruquintinib vs placebo in patients with mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy. Both trials met their primary endpoint and key secondary endpoint, with significantly prolonged OS (FRESCO HR: 0.65, 95% CI: 0.51, 0.83; p<0.001; FRESCO-2 HR: 0.66; 95% CI: 0.55, 0.80; p<0.001) and PFS (FRESCO HR: 0.26; FRESCO-2 HR: 0.32) with fruquintinib vs placebo. Additionally, fruquintinib resulted in a significant improvement in DCR vs placebo in both trials (FRESCO DCR: 62.2% vs 12.3%, p<0.001; FRESCO-2 DCR: 55.5% vs 16.1%; p<0.001), which is notable vs other therapies in previously treated mCRC based on a naïve, unanchored comparison (9, 10). In FRESCO, there was a significant increase in ORR with fruquintinib vs placebo (4.7% vs 0%, p=0.012) and in FRESCO-2, a numerical increase in ORR (1.5% vs 0%, p=0.059).

Overall, results were consistent between the two trials and are expected to be generalisable to patients the UK, which has been ratified by clinical experts at the UK oncologist advisory board (22nd September 2023) (11). FRESCO was conducted in an Asian population but only 30% of patients received prior VEGF inhibitors. In FRESCO-2, 96.5% patients received prior VEGF inhibitors, predominantly bevacizumab, which is not reimbursed in the UK, and patients enrolled in FRESCO-2 were more heavily pre-treated than in FRESCO. The advisors therefore concluded that FRESCO is more representative of current UK practice regarding prior exposure to anti-VEGF treatments, while FRESCO-2 enrolled patients that

were demographically more relevant to the UK with regard to age, race and geographical location (11). Therefore, both trials are highly relevant for clinical decision-making and together comprise an evidence base generalisable to the UK population.

Subgroup analyses in FRESCO and FRESCO-2 showed that an OS and PFS benefit for fruquintinib vs placebo was observed across nearly all prespecified subgroups. Notably in FRESCO, fruquintinib demonstrated a consistent improvement in OS vs placebo in patients without prior anti-VEGF therapies, which more closely reflects current UK clinical practice, where anti-VEGF therapies are unavailable. In relation to this, it has been hypothesised that prior exposure to anti-VEGF therapy may reduce the treatment effect of therapies with anti-VEGF activity, such as fruquintinib, given the mechanism of action targets some of the same anti-angiogenic pathways (18). The same statement was made during the appraisal of regorafenib (7). Therefore, FRESCO, FRESCO-2 and the pooled dataset may underestimate the true relative effect of fruquintinib vs BSC expected in a UK population due to the rate of prior exposure to anti-VEGF therapy in these datasets.

Similarly, in FRESCO-2, PFS and OS benefits were consistent irrespective of the number of previous lines of therapy for metastatic disease. The mean number of previous lines of therapy in the ITT population was 5.1 (standard deviation [SD]: 1.84) in the fruquintinib arm and 5.2 (SD: 1.94) in the placebo arm. Despite being used in more heavily pre-treated patients in FRESCO-2, the median OS benefit vs placebo was 2.6 months (HR: 0.66; 95% CI: 0.55, 0.80; p<0.001), compared with 2.7 months (HR: 0.65; 95% CI: 0.51, 0.83; p<0.001) in FRESCO, demonstrating a consistent treatment effect across the trials. Similarly, median PFS was 1.9 months longer with fruquintinib than with placebo in both studies. Hence, these data support the efficacy and tolerability of fruquintinib in heavily pretreated patients.

Moreover, in FRESCO-2, benefits with fruquintinib were seen regardless of previous treatment with trifluridine–tipiracil (>90% of patients) or regorafenib. As described in Dasari et al. (2023), these results are particularly relevant given that 48% of patients in FRESCO-2 had received previous treatment with regorafenib and suggest that inhibition of the VEGF pathway remains an important mechanism of disease control even in later-line settings. The higher target selectivity of fruquintinib compared with other approved anti-VEGF or anti-VEGFR therapies (18, 19) could explain the efficacy benefit observed in patients treated with fruquintinib, regardless of previous exposure to regorafenib.

In relation, whilst FRESCO-2 provides these data for patients who have received prior treatment with trifluridine–tipiracil and/or regorafenib, it is the only study of those identified by

the clinical SLR and included in the NMA which mandated prior receipt of these therapies. RECOURSE is the only study to report the proportion of patients who received prior regorafenib (17% and 20% of trifluridine-tipiracil- and placebo treated patients, respectively received prior regorafenib), with the remaining included studies not specifying. Therefore, receipt of prior trifluridine–tipiracil or regorafenib could not be explored or adjusted for within the NMA and is a limitation of the analysis (see below).

In both RCTs, fruquintinib was generally well tolerated, and any TEAEs were generally consistent with toxicities associated with VEGFR inhibitors. The tolerable safety profile of fruquintinib is thought to be linked to its unique MOA and its high selectivity compared with other VEGF inhibitors used in mCRC (19).

Patients who received fruquintinib stayed on treatment for almost twice as long as those who received placebo (FRESCO; median 3.7 months vs 1.8 months, FRESCO-2; median 3·1 months vs 1·8 months), consistent with the favourable efficacy and tolerability profile of fruquintinib.

Notably, fruquintinib was associated with low rates of fatigue, leukopenia, neutropenia and anaemia (leukopenia, neutropenia and anaemia being consistent with myelosuppression observed with trifluridine-tipiracil; Section B.3.4). Although Grade ≥3 adverse events occurred in 62.7% of patients in the fruquintinib arm vs 50.4% in the placebo arm (FRESCO-2), most AEs, including hypertension, asthenia, and hand-foot syndrome, were manageable with supportive care and dose modification. Specifically, clinicians do not regard hypertension as a TEAE of concern, and are used to treating it in the primary care setting (11), and rates of hand-foot syndrome for fruquintinib based on an unanchored, naïve comparison compare favourably with regorafenib (Section B.3.4).

The favourable adverse event profile of fruquintinib is further supported by an assessment of treatment exposure-adjusted event rates (EAERs) published by Howe et al, 2023 (129), for Grade 3/4 AEs associated with emerging and existing systemic therapies for mCRC with at least two prior lines of therapy. Based on this analysis, fruquintinib was found to have the lowest EAER rate per 1,000 patient-days (3.87) vs trifluridine-tipiracil (17.33) and regorafenib (16.70), and trifluridine-tipiracil + bevacizumab (4.19; note this treatment regimen is not yet available in the UK and subject to ongoing NICE appraisal ID6298). Findings indicate that fruquintinib is associated with lower rates of Grade 3/4 AEs (occurring in ≥5% of patients), relative to other systemic therapies.

Finally, maintaining the best possible HRQoL, while prolonging survival, is one of the main aims of treatment for mCRC (15). In FRESCO-2, HRQoL was measured by QLQ-C30 global health and EQ-5D-5L, and was not negatively impacted by treatment with fruquintinib, and fruquintinib delayed time-to-deterioration in QoL compared with placebo for QLQ-C30 subscales and EQ-5D-5L VAS metrics.

These results, along with the statistically and clinically meaningful improvement of OS and PFS and manageable toxicity profile, further support fruquintinib as a potential new treatment option for patients with previously treated mCRC.

The evidence base for fruquintinib is further strengthened by a number of real world evidence (RWE) studies (Appendix D, Section D.2.4) given its approval for use in China since 2018. These studies support the efficacy and safety conclusions for fruquintinib from the FRESCO and FRESCO-2 RCTs (70-82). From the identified observational studies of fruquintinib, median OS was numerically (71, 77) or significantly (72) longer for fruquintinib than for regorafenib. Median OS for fruquintinib ranged from 9-12 months (in studies without any comparator arm (76, 78)), 7.4-9.3 months (in the fruquintinib arm of the RCTS (63, 83, 130)) and 7.8-13.8 months (in studies vs regorafenib (88, 89, 99)). Notably, the difference was significant in one study (72), where fruquintinib was associated with median OS of 11.3 months vs 10 months for regorafenib.

A key limitation of the analysis is that there are no head-to-head data comparing fruquintinib to trifluridine-tipiracil and regorafenib. Therefore, an NMA was conducted to synthesise relative treatment effects for OS and PFS using all eight RCTs identified by the clinical SLR for the treatments listed in the NICE scope (20), as considered appropriate following a feasibility assessment. The NMA was conducted in line with the recommendations in the NICE Decision Support Unit (DSU) technical support documents (TSD) 2 (120), TSD 3 (123), and TSD 18 (121).

Where imbalances in patient baseline characteristics between included RCTs were identified, an assessment was conducted to determine whether these were potential treatment effect modifiers. Although exposure to prior anti-VEGF treatment was considered the only likely effect modifier in mCRC, experts at the UK market access advisory board (1st December 2023) stated it was unnecessary to adjust for treatment effect modifiers at this late line of treatment and advised that a standard NMA, without any formal adjustment for treatment effect modifiers, was most appropriate. The FE model was selected for the base case analysis after evaluation of the DIC; enhanced convergence and minimal

autocorrelation were prioritised, supported by visual examination of density and trace plots. Given fewer than five studies per treatment comparison, the FE model was considered more reliable than the RE model. The FE approach and results were aligned with those presented in prior HTAs in mCRC.

NMA results showed that fruquintinib was associated with a significant improvement in both OS and PFS vs BSC (HR: 0.66 [95% CrI 0.57, 0.76] and HR: 0.30 [95% CrI 0.26, 0.34], respectively). These results were consistent with the observed data in the FRESCO and FRESCO-2 RCTs, the results of the pooled analyses and the results estimated by the pairwise meta-analysis.

In addition, results showed that fruquintinib was associated with a significant reduction in the risk of progression or death vs active comparators (HR: 0.66 [95% CrI: 0.54, 0.81] vs regorafenib and 0.67 [95% CrI: 0.55, 0.80] vs trifluridine-tipiracil), with the likelihood of fruquintinib ranking first in the network ahead of trifluridine-tipiracil and regorafenib at 100%. For OS, fruquintinib was associated with a numerical improvement vs active comparators (HR: 0.93 [95% CrI: 0.75, 1.16] vs regorafenib and 0.95 [95% CrI: 0.78, 1.15] vs trifluridine-tipiracil), with the likelihood of fruquintinib ranking first in the network ahead of trifluridine-tipiracil and regorafenib at 81%. Results of the NMA (fruquintinib, regorafenib and trifluridine-tipiracil vs BSC) were consistent with the observed data reported in key clinical trials contributing to the analysis and outcomes of the NMA presented in TA866. A series of scenario analyses were conducted for both OS and PFS, and yielded highly consistent results versus the base case analysis, demonstrating robustness of results and the minimal impact of between-trial imbalances in baseline patient characteristics and potential effect modifiers on results.

B.2.12.2 Overall conclusions

Fruquintinib provides an alternative treatment option for [redacted] As demonstrated by the FRESCO and FRESCO-2 studies (Section B.2.6.2), fruquintinib results in statistically significant improvements in both OS and PFS vs placebo. Results were consistent between the two trials and are expected to be generalisable to patients the UK, based on the UK oncologist advisory board (22nd September 2023) (11) (Section B.2.12.1).

Fruquintinib offers a convenient, oral, once-daily mode of administration, a manageable safety profile, and leads to extended maintenance of HRQoL vs placebo, as measured by pre-specified QoL assessments (20). Additionally, based on clinical expert feedback from the UK market access advisory board (1st December 2023) (47), fruquintinib offers a favourable safety profile when compared to current recommended treatments, particularly regorafenib, which has known toxicity issues.

Overall, the results from FRESCO, FRESCO-2, and the NMA support fruquintinib as a new oral, alternative treatment option for patients with mCRC who have previously received at least two treatments. The observed efficacy of fruquintinib in these patients is consistent across patient populations and studies, including patients previously treated with trifluridine-tipiracil and regorafenib. The availability of fruquintinib would add to the armamentarium for patients with previously treated mCRC and enrich the continuum of care for this patient group (63).

B.3 Cost effectiveness

Fruquintinib is a cost-effective therapy in patients [redacted], at a willingness-to-pay (WTP) threshold of £51,000 per quality-adjusted life year (QALY) gained

- A cost-utility analysis with a lifetime (10-years) time horizon was conducted to evaluate the cost-effectiveness of fruquintinib vs regorafenib, trifluridine-tipiracil, and BSC in England and Wales
- The population evaluated aligns with the anticipated marketing authorisation of fruquintinib; patients with metastatic CRC 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 model was an area under the curve (AUC) partitioned survival model (PSM), comprised of three mutually exclusive health states: progression-free, post-progression, and death
- Clinical inputs for fruquintinib and BSC were informed by pooled data from the two pivotal clinical trials, FRESCO and FRESCO-2. Individual patient data (IPD) from FRESCO-2 were analysed to inform health state utility values
- Parametric curves were fitted to PFS, OS and TTD KM curves for fruquintinib, and to PFS and OS KM curves for BSC
- In the absence of direct evidence comparing the efficacy of fruquintinib with regorafenib and trifluridine-tipiracil, an NMA was conducted. The resulting HRs vs fruquintinib were used to predict PFS and OS for regorafenib and trifluridine-tipiracil
- BSC costs comprised those associated with concomitant medications, medical resource use and terminal care
- In the base case (including the proposed patient access scheme [PAS] price), fruquintinib was associated with cost savings of £[redacted] and an incremental QALY gain of [redacted] vs regorafenib, meaning fruquintinib was dominant when compared with regorafenib
- Clinical experts advised that trifluridine-tipiracil monotherapy is expected to be replaced by trifluridine-tipiracil in combination with bevacizumab, and the majority of fruquintinib use in UK clinical practice would be in replacement of regorafenib, therefore the comparison with regorafenib is the most relevant for decision making; a pairwise comparisons with BSC is presented to reflect the limited number of patients who have been previously treated with or are not considered candidates for trifluridine-tipiracil and/or regorafenib.
- At the proposed PAS price, fruquintinib was associated with incremental costs of £[redacted] and £[redacted], incremental QALY gains of [redacted] and [redacted], and resulting

pairwise incremental cost-effectiveness ratios (ICER) of [redacted] and [redacted] vs trifluridine-tipiracil and BSC, respectively

- Proportional QALY shortfalls of 0.96, 0.96 and 0.97 for regorafenib, trifluridine-tipiracil and BSC respectively, indicates that a £51,000 WTP threshold is appropriate for the comparison with all comparators

B.3.1 Published cost-effectiveness studies

An SLR was conducted on 23rd October 2023 to identify economic evaluations in patients with 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, if *RAS* wild type, an anti-EGFR therapy. A detailed description of the SLR methods, full results and quality assessment of the identified economic evaluations is presented in Appendix G.

A total of 41 economic evaluations (reported in 41 publications) were identified by the SLR. The PRISMA flow diagram and full list of included publications are provided in Appendix G (Sections G.2.1 and G.2.5.1, respectively). Of these, there were three economic evaluations of fruquintinib: one assessed the cost-effectiveness of fruquintinib vs regorafenib for the treatment of mCRC who have had two or more previous treatments from a Chinese health care perspective (131); and two assessed the cost-effectiveness of fruquintinib vs BSC for the treatment of mCRC who have had two or more previous treatments from a Chinese health care perspective (132) or from a Chinese societal perspective (133).

Although the SLR was not restricted by geographical region, analyses of treatments specified in the NICE final scope for the population of interest and conducted from a UK perspective were considered the most relevant for informing the decision problem for this appraisal. Of the 41 identified publications, four economic evaluations (7, 55, 134, 135) were conducted from a UK healthcare perspective: one peer-reviewed publication (134) and three health technology assessment (HTA) submissions (7, 55, 135), which are described below (Table 28:).

Of the four UK economic evaluations: three compared trifluridine-tipiracil with regorafenib (160 mg dose once daily) and BSC (55, 134, 135) (note that the evaluation reported in Bullement [2018] was linked to NICE TA405 (55)); one economic evaluation compared regorafenib with BSC (TA866). All models used a partitioned survival model with a three-state model structure characterised by progression-free/pre-progression, progression and death and evaluated costs and QALYs from a UK NHS perspective over a 10-year (lifetime) time horizon (7, 55, 134-136). Clinical efficacy data were taken from the key trials available

for regorafenib and trifluridine-tipiracil. Other model inputs used in these analyses, including costs and healthcare resource use, and utilities alongside results, are summarised in Appendix G. The modelling approaches adopted in the UK economic evaluations were considered during model development (Section B.3.2).

Table 28: Summary list of economic evaluations from a UK NHS perspective

Study Country	Patient population	Model structure	Interventions	Incremental costs (£)	Incremental QALYs	ICER cost (£)/QALY gained
Bullement 2018 (UK) (134)	Patients with mCRC who have been previously treated with or are not eligible for fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, an anti-VEGF therapy, and an anti-EGFR therapy	PSM with three health states: 1. Pre-progression 2. Progressed disease 3. Death	Regorafenib (160 mg dose once daily) vs trifluridine-tipiracil vs BSC	• Trifluridine-tipiracil vs BSC: 8,479 (95% CI: 7,959, 9,011) • Regorafenib vs BSC: 14,613 (95% CI: 12,027, 17,642) • Regorafenib vs trifluridine-tipiracil: 6,134 (95% CI: 3,554, 9,214)	• Trifluridine-tipiracil vs BSC: 0.17 (95% CI: 0.11, 0.22) • Regorafenib vs BSC: 0.11 (95% CI: –0.01, 0.26) • Regorafenib vs trifluridine-tipiracil: -0.06 (95% CI: –0.16, 0.08)	• Trifluridine-tipiracil vs BSC: 51,194 • Regorafenib vs BSC 133,561 • Regorafenib vs trifluridine-tipiracil: trifluridine tipiracil dominates
NICE TA866 (regorafenib) (7)	People with mCRC who have progressed on 1st line treatment and are being considered for 3rd line plus treatment	PSM with three health states: 1. Progression free 2. Progressed disease 3. Death	Regorafenib vs trifluridine-tipiracil vs BSC	Costs are reported as commercial in confidence	QALYs are reported as commercial in confidence	ICERs are reported as commercial in confidence
NICE TA405 (trifluridine-tipiracil) (55)	Adult patients with mCRC, previously treated with and not considered eligible for available therapies including FU-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF biological therapies, and anti-EGFR therapies	PSM with three health states: 1. Pre-progression 2. Post-progression 3. Death	Trifluridine-tipiracil vs regorafenib (160 mg dose once daily) vs BSC and vs regorafenib (sensitivity analysis)	Base-case results with PAS: trifluridine-tipiracil 16,386; BSC: 10,286 Incremental costs trifluridine-tipiracil vs BSC: 7,574	Trifluridine-tipiracil 0.59; BSC 0.42 Incremental QALYs trifluridine-tipiracil vs BSC: 0.17	Base-case results with patient access scheme trifluridine-tipiracil vs BSC: 44,032
SMC 1221-17 (trifluridine-tipiracil) (135)	Adult patients with mCRC, previously treated with and not considered eligible for available therapies including FU, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF agents, and anti-EGFR agents	PSM with three health states: 1. Pre-progression 2. Post-progression 3. Death	Trifluridine-tipiracil vs BSC	Base-case results with PAS: incremental costs trifluridine-tipiracil vs BSC: 8,197	Base-case results with PAS: incremental costs trifluridine-tipiracil vs BSC: 0.17	Base-case results with PAS trifluridine-tipiracil vs BSC 49,225

Abbreviations: BSC, best supportive care; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FU, fluorouracil; ICER, incremental cost-effectiveness ratio; mCRC, metastatic colorectal cancer; NR, not reported; PAS, patient access scheme; PSM, partitioned survival model; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium; UK, United Kingdom; VEGF, vascular endothelial growth factor; vs, versus.

B.3.2 Economic analysis

Three existing economic evaluations of fruquintinib were identified by the cost-effectiveness SLR (Section B.3.1). All three identified studies assessed fruquintinib from either the Chinese health care perspective or the Chinese societal perspective. Due to the differences in health care systems between China and England and Wales, a *de novo* cost-effectiveness analysis relevant to the decision problem considered in this submission was developed.

The SLR of economic evaluations reported in Section B.3.1 was used to inform inputs and assumptions in the *de novo* cost-effectiveness model. Of the four UK economic evaluations, three were prior UK HTAs: two NICE appraisals (TA405 (55) and TA866 (7)) and a Scottish Medicines Consortium (SMC) submission of trifluridine-tipiracil (135); note that due to limitations in reporting in the latter, this was not considered further in the model development process. Section B.3.2.2 describes how these HTAs specifically informed the development of the *de novo* model for this appraisal.

B.3.2.1 Patient population

The population considered in the cost-effectiveness analysis is [redacted]. This is in line with the anticipated marketing authorisation of fruquintinib (Appendix C).

B.3.2.2 Model structure

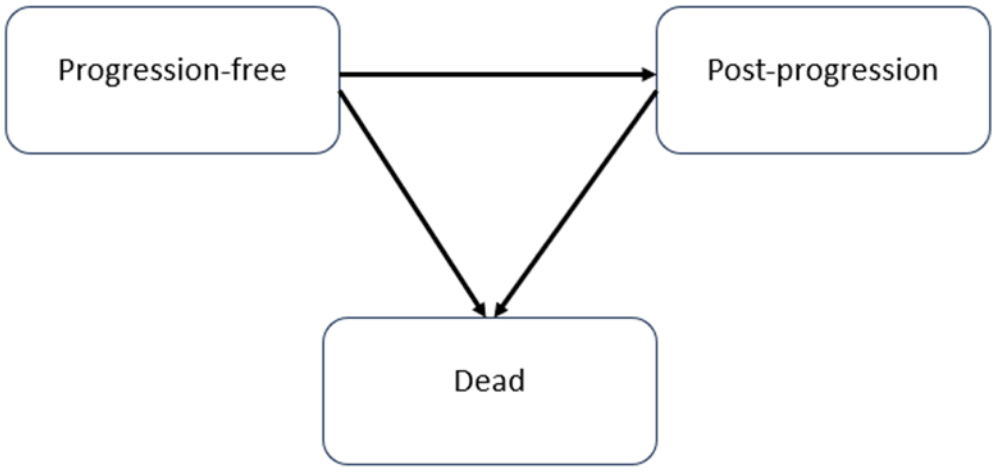
The *de novo* cost-effectiveness model was developed in Microsoft® Excel 2019 using an area-under-the-curve (AUC), partitioned survival model (PSM) approach. The model comprises three mutually exclusive health states; progression-free, post-progression, and dead (Figure 28). Progression-based models are common in economic analyses of oncology treatments as they accurately reflect the progressive nature of the disease with separate pre- and post-progression states and reflect the clinical pathway of care in mCRC. The model structure is also consistent with previous HTAs in mCRC, including the trifluridine-tipiracil (TA405) and regorafenib (TA866) NICE appraisals, and has been accepted as appropriate for decision-making by NICE (7, 55).

Health state occupancy over time is informed directly by the area under the OS and PFS curves for each comparator. The area under the PFS curve informs the proportion of patients residing in the ‘progression-free’ health state over time. The area under the OS curve informs the proportion of patients who are alive. The proportion of patients who are

alive with progressed disease, and hence reside in the 'post-progression' health state, is calculated as the area between the OS curve and the PFS curve. Costs and QALYs were accrued according to the proportion of patients in the 'progression-free' and 'post-progression' health states over time.

PFS and OS are modelled independently (i.e. using independent parametric functions). Therefore, to retain face validity and prevent the PFS curve from being able to lie above the OS curve, the extrapolated PFS curve was capped by the OS curve. In addition, PFS and OS are capped by general population mortality informed by life tables for England and Wales (137) to ensure that modelled patients do not have a lower risk of death compared with the general population.

Figure 28: Model schematic



B.3.2.3 Time horizon

The cost-effectiveness model adopted a 'lifetime' time horizon. NICE guidance states the model time horizon should be sufficiently long to reflect all differences in costs and outcomes between technologies over a patient's lifetime (138). Due to the poor outcomes of patients with mCRC, fewer than 0.5% of patients remain alive in the model at 10 years. Therefore, a 10-year lifetime horizon was used in the base case analysis. A 10-year time horizon was also used in previous TAs in mCRC (44, 53). A shorter time horizon of 5 years was explored in scenario analyses.

B.3.2.4 Cycle length

The model adopted a weekly cycle length to accurately capture the costs and HRQoL impact of fruquintinib and the relevant comparators. A half-cycle correction was applied using the life table method to account for uncertainty in the timing of transitions within the cycle period,

where time in each cycle was estimated using the average of the number of people at the start and end of the cycle.

B.3.2.5 Discounting

In the base case, a discount rate of 3.5% per annum was applied to costs and benefits in line with the NICE reference case (138). Discount rates of 0% and 1.5% were explored in scenario analyses.

B.3.2.6 Perspective

The analysis was conducted from the perspective of the NHS and personal social services (PSS) in England and Wales, in line with the NICE reference case (138).

B.3.2.7 Features of the economic analysis

Key features of this economic analysis, as well as the approaches taken in all previous NICE appraisals in previously treated mCRC, are outlined in Table 29. As highlighted in Section B.3.1, the most relevant appraisals for this analysis are trifluridine-tipiracil (TA405) (55), and regorafenib (TA866) (7) as they are both relevant comparators for fruquintinib and align with the population for this appraisal (Section B.3.2.8.2). The approach taken in other late stage mCRC appraisals is presented for completeness.

Table 29: Features of the current economic analysis relative to previous NICE appraisals in mCRC

Factor	Previous appraisals†					Current appraisal	
	TA242 (cetuximab, bevacizumab, panitumumab) (139)¶	**TA307 (aflibercept in combination with irinotecan and fluorouracil-based therapy) (140)††**	**TA405 (trifluridine-tipiracil) (44)**	**TA668 (encorafenib plus cetuximab) (68)‡**	**TA866 (regorafenib) (53)**	**Chosen approach**	**Justification**
Model type	CUA (PSM)	CUA (PSM)	CUA (PSM)	CUA (PSM)	CUA (PSM)	CUA (PSM)	The NICE reference case specifies CUA as the preferred form of economic evaluation (138)
Time horizon	10 years	15 years	10 years	10 years	10 years	10 years (lifetime)	The NICE reference case (138) recommends a lifetime horizon to capture all expected differences in costs and benefits between treatments. Given a starting age of 59.21 years, and the poor survival in this patient population, by 10 years <0.5% of patients are alive in the fruquintinib arm of model
Model cycle length	1 month	2 weeks	1 day	1 month	1 week	1 week	Accounts for the different dosing schedules for relevant comparators and is sufficiently short to capture all relevant difference between fruquintinib and the comparators
Treatment effect waning	Not described	Not described	Not described	None	None	None	Any assumption of the waning of treatment effect would be applied equally to each of the comparators relative to BSC risks. No treatment effect waning was applied for regorafenib or trifluridine-tipiracil in TA866 (7, 55), therefore this assumption aligns

Factor	Previous appraisals†					Current appraisal	
	TA242 (cetuximab, bevacizumab, panitumumab) (139)¶	**TA307 (aflibercept in combination with irinotecan and fluorouracil-based therapy) (140)††**	**TA405 (trifluridine-tipiracil) (44)**	**TA668 (encorafenib plus cetuximab) (68)‡**	**TA866 (regorafenib) (53)**	**Chosen approach**	**Justification**
							with committee accepted assumptions
Source of utilities	CO.17 trial	mCRC utilities study	CORRECT trial	BEACON trial	Pooled CORRECT and CONCUR EQ-5D data	EQ-5D-5L from FRESCO-2 trial mapped to EQ-5D-3L	Uses HRQoL data collected from a large Phase III RCT assessing the intervention and population relevant to the decision problem, as per NICE reference case (138)
Source of costs resource use	BNF/NHS reference costs	Clinical study, BNF, PSSRU, NHS reference costs	SLR, BNF, PSSRU, NHS reference costs	SLR, BNF, PSSRU, NHS reference costs, eMIT, clinical input	SLR, BNF, PSSRU, NHS reference costs, eMIT, clinical input	SLR, BNF, PSSRU, NHS reference costs, eMIT, clinical input, previous NICE appraisals	As per NICE reference case (138)

Note, the date remit for the assessment of prior appraisals was broader (any previously treated mCRC appraisals) than for the SLR (published between 2020 and 2023) reported in Section B.3.1.

†The scope for review of prior technology appraisals for the assessment of model structure was broader than the inclusion criteria for the SLR (Section B.3.1): assessed cost-effectiveness of interventions not in PICO in the second-line population

‡The HTA of encorafenib + cetuximab (68) undertaken by NICE was not included in the SLR of economic evaluations (Section B.3.1) as there were no extractable outcome data in the committee papers (data redacted)

¶The HTA of cetuximab, bevacizumab, and panitumumab was not identified in the SLR due to the date limit for searches of HTA agency websites (publications 2020-2023) but Hoyle 2013 (136) reported the EAG model from that appraisal

††The HTA of aflibercept (140) was not identified in the SLR due to the date limit for searches of HTA agency websites (publications 2020-2023)

Abbreviations: BNF, British National Formulary; BSC, best supportive care; CUA, cost utility analysis; EAG, external assessment group; eMIT, electronic marketing information tool; EQ-5D-3L, EuroQol five-dimension three-level; EQ-5D-5L, EuroQol five-dimension five-level; HRQoL, health-related quality of life; HTA, health technology appraisal; mCRC, metastatic colorectal cancer; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PartSA, Partitioned survival analysis; PICO, patient/population, intervention, comparison and outcomes; PSM, partitioned survival model; PSSRU, Personal Social Services Research Unit; RCT, randomised controlled trial; SLR, systematic literature review; TA, technology appraisal.

B.3.2.8 Intervention technology and comparators

B.3.2.8.1 Intervention

The intervention considered in this analysis is fruquintinib, which is administered orally at a recommended dose of 5 mg QD following a dosing schedule of three weeks on and one week off as per the dosing regimen received in FRESCO and FRESCO-2, and the anticipated marketing authorisation for fruquintinib, combined with BSC (44, 53). Treatment with fruquintinib should be continued until disease progression or unacceptable toxicity occurs.

B.3.2.8.2 Comparators

As described in Section B.1.3.4, the relevant comparators for this analysis are regorafenib, trifluridine-tipiracil, and BSC, which aligns with the NICE final scope (20). Similar to fruquintinib, the costs of BSC were included in the regorafenib and trifluridine-tipiracil arms.

Of note, throughout Section B.2, the term “placebo” was used to describe the placebo + BSC arms in FRESCO and FRESCO-2 to align with the terminology used in the clinical study reports and clinical publications. In this appraisal, these placebo + BSC arms have been used to represent the BSC comparator.

Therefore, the relevant comparators for this appraisal are:

- Regorafenib administered orally at the SmPC recommended dose of 160 mg (4 x 40 mg tablets) QD for 3 weeks followed by 1 week off therapy until there is no observed benefit or until unacceptable toxicity occurs. This dose is also aligned with dosing schedules in the CORRECT and CONCUR clinical trials

- Trifluridine-tipiracil 35 mg/m^2 orally twice daily, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period. This treatment cycle is repeated every 4 weeks until disease progression or unacceptable toxicity. This dose is also aligned with the dosing schedule in the TERRA and RECOURSE clinical trials and the SmPC for trifluridine-tipiracil (141)

- BSC was defined within the FRESCO and FRESCO-2 trial protocol as any treatment necessary for health and not anticipated to interfere with study drug and was determined locally by the investigator. BSC therefore excluded other anti-tumour agents, radiotherapy (except palliative radiation), biotherapy, endocrine therapy, or any other study drug treatment. Clinicians advised that the medications received as part of BSC in FRESCO and FRESCO-2 were generally consistent with UK clinical

practice, and any differences between the BSC arms of FRESCO/FRESCO-2 and UK clinical practice would not be expected to impact on patient outcomes. Clinicians also advised that the definition of BSC in FRESCO and FRESCO-2 was consistent with the pivotal trials for regorafenib and trifluridine-tipiracil (47).

Of note, a fully incremental analysis was conducted per the NICE reference case, comparing fruquintinib with regorafenib, trifluridine-tipiracil, and BSC. However, feedback from clinical experts at the market access advisory board stated that trifluridine-tipiracil monotherapy is expected to be replaced in the near future by trifluridine-tipiracil in combination with bevacizumab (assuming a positive NICE recommendation from the ongoing appraisal ID6298)(142), so the majority of fruquintinib use in UK clinical practice is expected to replace the use of regorafenib (11). Therefore, the most relevant comparison for decision making was deemed to be a pairwise comparison vs regorafenib. A pairwise comparison vs BSC is also presented to reflect the patients who have been previously treated with or are not considered candidates for trifluridine-tipiracil and/or regorafenib.

B.3.3 Clinical parameters and variables used in the economic model

Both large, Phase III randomised, placebo-controlled trials assessing fruquintinib in the relevant population, FRESCO and FRESCO-2, were used to inform the clinical inputs for fruquintinib and BSC in the economic model (44, 53). As discussed in Section B.2.6.3, the two trials were pooled and were used to inform modelled patient baseline characteristics, OS, PFS, and TTD for fruquintinib, OS and PFS for BSC, AE rates, RDI and subsequent therapies.

B.3.3.1 Baseline characteristics

Modelled patient baseline characteristics derived from the pooled FRESCO and FRESCO-2 studies are presented in Table 30. The mean age at baseline was 59.4 years, mean patient body weight was 70.17 kg, and mean BSA was 1.78 m^2. The proportion of male patients across the two trials was 57.8%.

To explore uncertainty, one-way sensitivity analysis was conducted which varied these modelled patient characteristics. Cost-effectiveness results were not sensitive to these analyses.

Table 30: Baseline characteristics

Variable	Value	Source
Baseline age, years	59.4 (SD=10.98)	FRESCO and FRESCO-2 pooled data (116)
Male, %	57.8%	
Body weight, kg	70.17 (SD=16.06)	
BSA, m^2	1.78 (SD=0.21)	

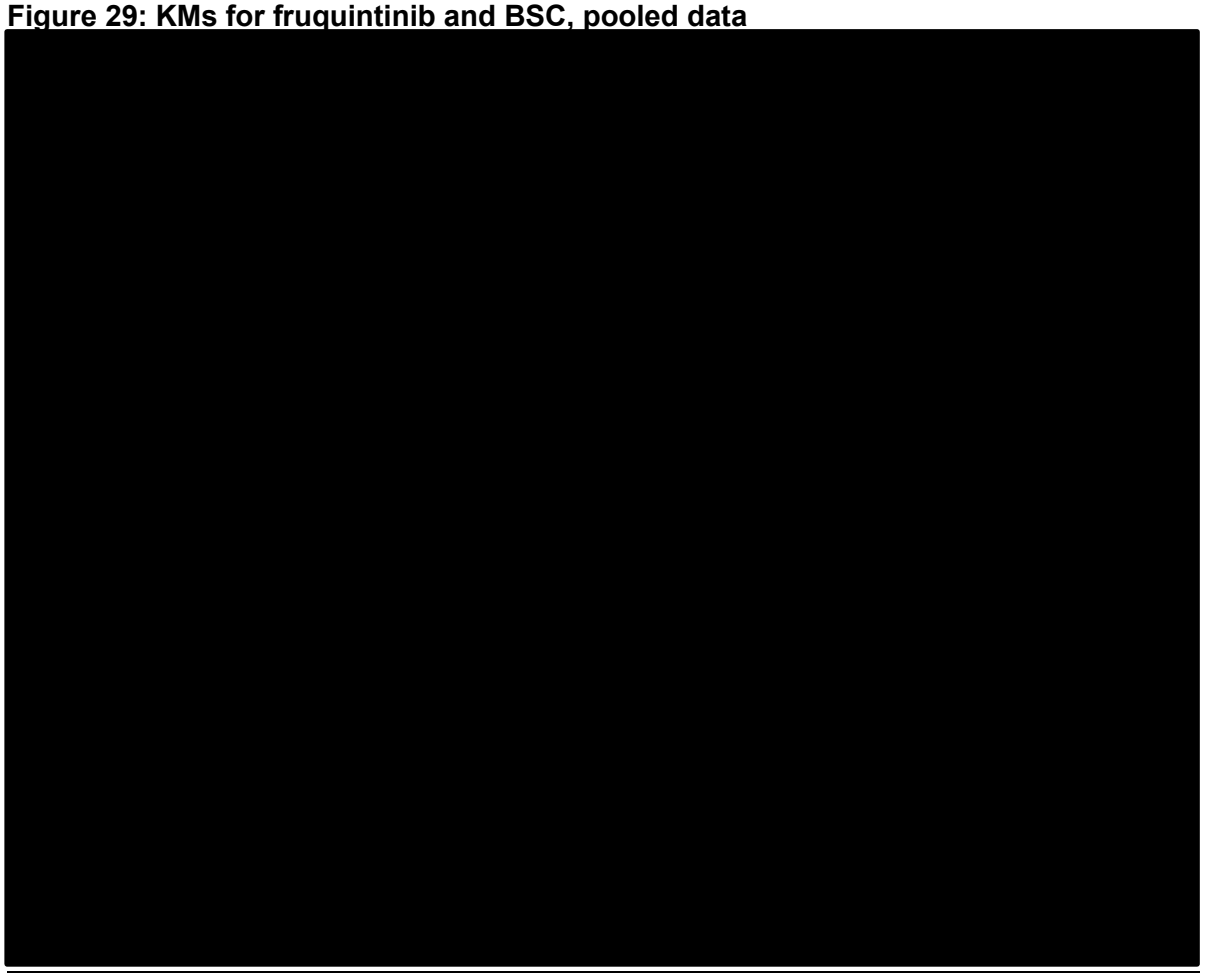
Abbreviations: BSA, body surface area; SD, standard deviation.

B.3.3.2 Survival extrapolation

Clinical efficacy estimates for fruquintinib and BSC were informed by the pooled FRESCO and FRESCO-2 data (Section B.2.6.3). Parametric distributions were fitted to pooled PFS, OS, and TTD KM curves for fruquintinib, and to pooled PFS and OS KM curves for BSC, to extrapolate these data over a lifetime time horizon. Seven standard parametric survival distributions were fitted to the pooled KM data: exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma and gamma. The most appropriate parametric distribution for each endpoint was selected based on an assessment of goodness-of-fit statistics, visual fit to the observed data, clinical expert validation of long-term extrapolations, and comparison with published real-world data where available. This aligns with the recommended approach outlined in the NICE DSU TSD 14 (143).

TTD was not modelled for BSC, as it was assumed that there are no treatment acquisition costs associated with BSC other than concomitant medications and healthcare resource use, as per TA866 (Section B.3.6.2). The pooled PFS, OS, and TTD KM data for fruquintinib and PFS and OS KM data for BSC are presented in Figure 29.

Figure 29: KMs for fruquintinib and BSC, pooled data



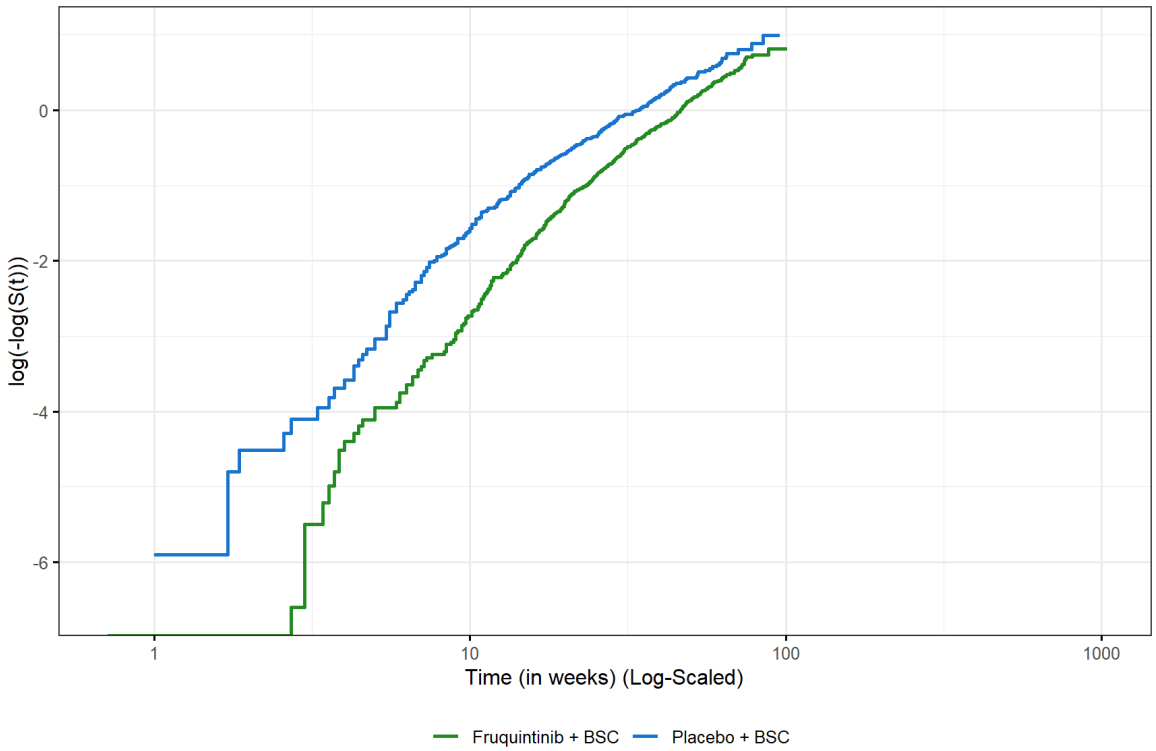
Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

B.3.3.2.1 Overall survival

Figure 30 presents the log-cumulative hazard plot for fruquintinib and BSC. The plot is relatively parallel throughout, and the curves do not cross suggesting there is no violation of the proportional hazards (PH) assumption. Figure 32 presents the quantile-quantile plot for OS, with the points showing a relatively straight line, suggesting no violation of the accelerated failure time (AFT) assumption. Therefore, the assumption of a constant treatment effect was considered to be appropriate in the base case. Similarly, the smoothed hazard plot (Figure 33) show a similar hazard shape over time, with the risk of death increasing initially, then decreasing over time. Furthermore, clinical experts at the UK market access advisory board (1st December 2023) (11) advised that they wouldn't expect any difference in how hazards change over time, as neither treatment is changing the course of the disease. Therefore, in the base case, fruquintinib and BSC OS were extrapolated using a joint parametric model, assuming baseline risks estimated from the BSC arm with a covariate for treatment with fruquintinib. The global test of the PH assumption provided a p-value less than 0.05, meaning that the null hypothesis of PH was rejected at the 95% level of

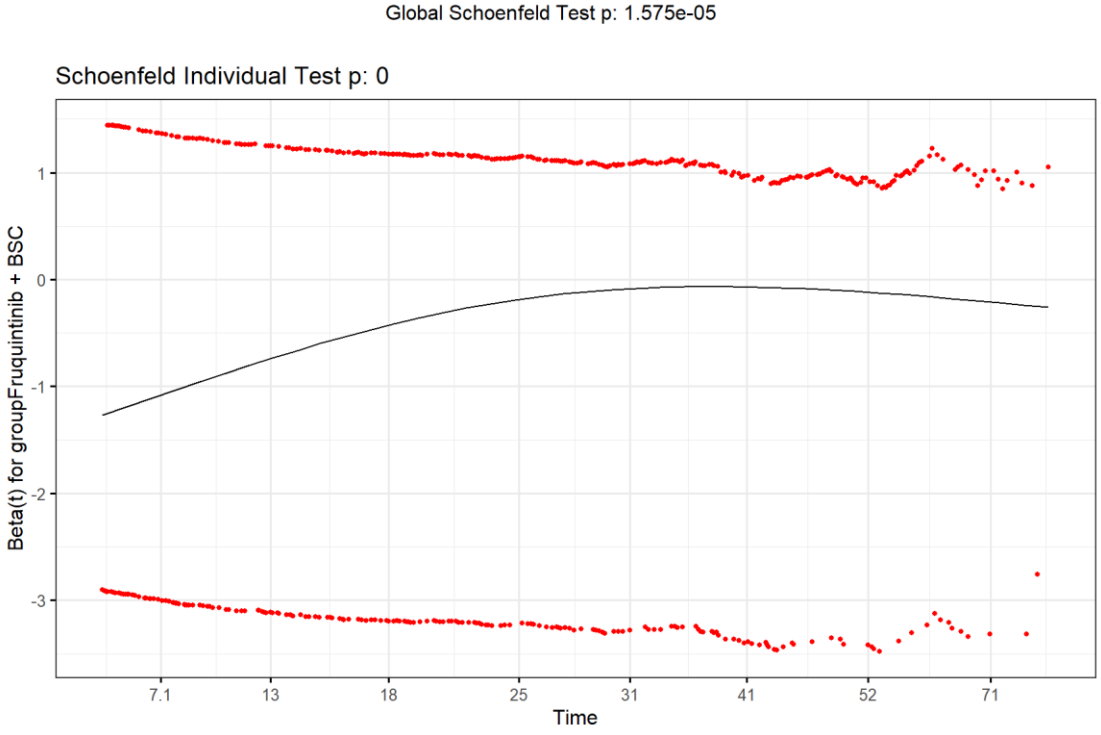
confidence (Figure 31), and therefore scenario analyses were conducted where fruquintinib and BSC OS were extrapolated using independent parametric models.

Figure 30: Log cumulative hazard plot, pooled data, OS



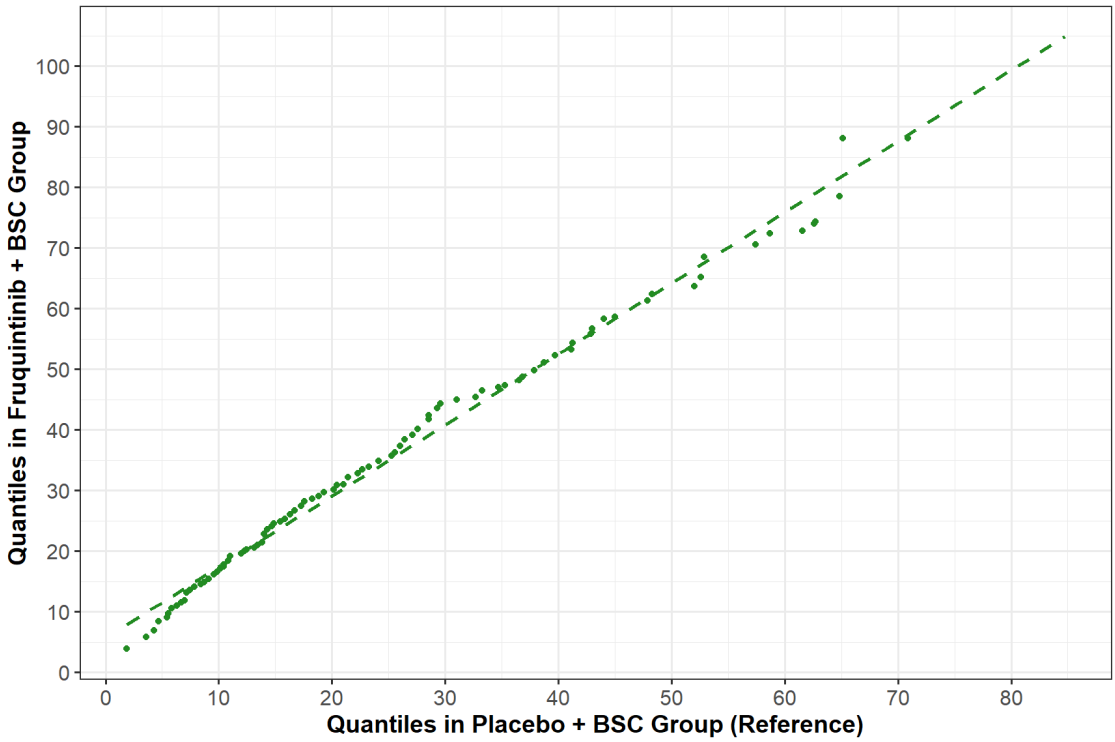
Abbreviations: BSC, best supportive care; OS, overall survival.

Figure 31: Schoenfeld residual plot, pooled data, OS



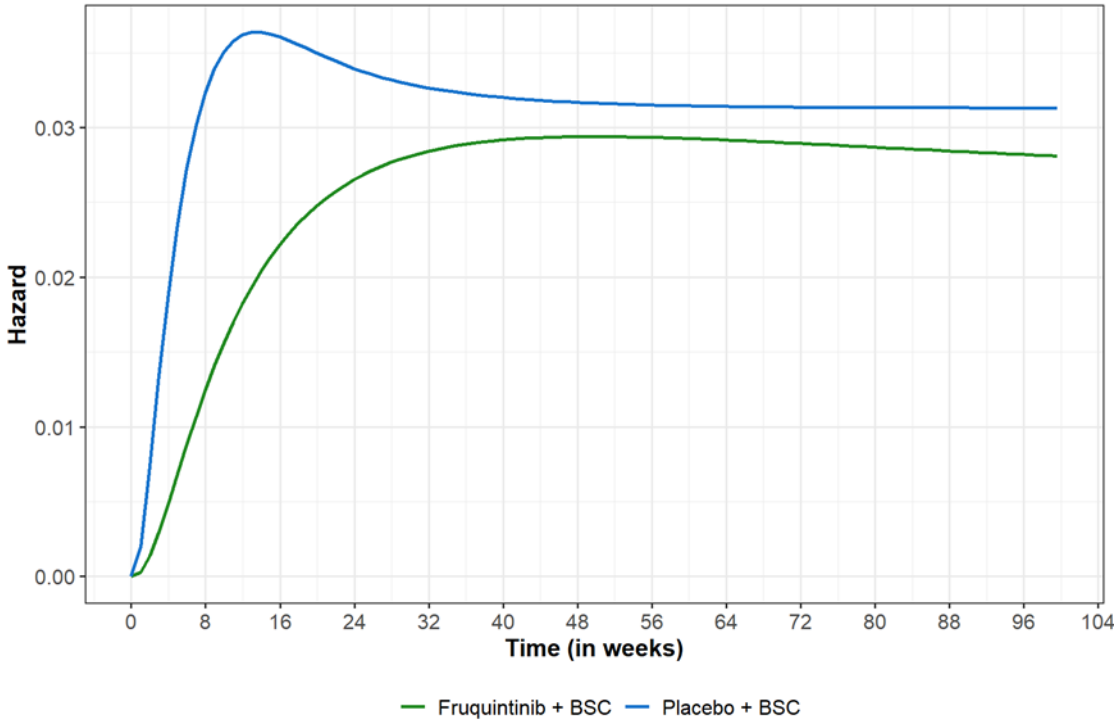
Abbreviations: BSC, best supportive care; OS, overall survival.

Figure 32: Quantile-quantile plot, pooled data, OS



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

Figure 33: Smoothed hazard plot, pooled data, OS



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

Figure 34 and Figure 35 present the OS parametric distributions and KM curves for fruquintinib and BSC, respectively. OS KM data for fruquintinib and BSC were mature at data cut-off, with 68.3% and 76.6% of patients having experienced an OS event at the end of

follow-up (23.3 months) in the fruquintinib and BSC arms, respectively. The log-normal, generalised gamma, and log-logistic joint models were associated with the best statistical fit based on minimisation of the Akaike information criteria (AIC) and Bayesian information criteria (BIC) statistics of the seven parametric curves that were fitted (Table 31).

On visual inspection, for fruquintinib, all curves appeared to provide a good fit to the observed data in the first 12 months, except for the Gompertz and exponential distributions, which underpredicted survival vs the observed data. Of the remaining distributions, towards the end of the observed data, the log-logistic (2-year OS: [redacted]%), log-normal (2-year OS: [redacted]%), and generalised gamma (2-year OS: [redacted]%) curves provided estimates consistent with the observed data (23.3-month OS: [redacted]%) which further supported the selection of these curves. For BSC, the Weibull, gamma and Gompertz distributions underpredicted survival, and the remaining distributions all appeared to have little difference between them with respect to visual fit.

Figure 34: Parametric fits for OS (joint models) compared with KM data, fruquintinib, pooled data

Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Figure 35: Parametric fits for OS (joint models) compared with KM data, BSC, pooled data

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival

Table 31: OS goodness-of-fit statistics for fruquintinib and BSC (joint models), pooled data

Distribution	Fruquintinib and BSC	
	AIC	BIC
Exponential	7517.6	7527.6
Weibull	7384.6	7399.6
Gompertz	7459.1	7474.1
Log-logistic	7339.6	7354.6
Log-normal	7335.4	7350.4
Gamma	7358.8	7373.9
Generalised gamma	7335.5	7355.5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; OS, overall survival.

Landmark estimates of OS for each distribution and the observed data are presented in Table 32 and Table 33, for fruquintinib and BSC, respectively. For both fruquintinib and BSC, most of the distributions predicted similar 5-year survival due to the maturity of the FRESCO and FRESCO-2 data. Clinical expert opinion elicited during the UK market access advisory board (1st December 2023) (11) advised that for BSC, 4% of patients would be alive at two years in clinical practice, and 0% of patients would be expected to be alive at five years. This is consistent with the OS landmark estimates predicted by the generalised gamma

distribution at two and five years, which predicted survival to be [redacted]% and [redacted]%, respectively, with BSC.

As BSC outcome data are reported across the published literature for mCRC (i.e. in the eight RCTs identified in the SLR that informed the NMA, as described in Section B.3.1), predicted outcomes for each BSC curve were compared with observed medians reported in relevant RCTs and with modelled outcomes, based on committee preferred assumptions, reported in TA405 and TA866 (7, 55). The predicted median OS values, based on all seven distributions, were consistent with the observed median OS data reported in the RCTs for BSC, which ranged from 5.0 months (CORRECT) to 7.1 months (TERRA) (10, 109). Similarly, there was consistency in the median and landmark estimates of BSC OS reported in TA405 and TA866 with the predicted OS estimates with the log-logistic, log-normal and generalised gamma distributions (Table 33).

Therefore, a joint generalised gamma distribution was chosen for the base case extrapolation as it provided a good statistical and visual fit to the observed fruquintinib and BSC data, provided clinically plausible long-term estimates of survival, as per clinical expert opinion, and provided predicted median and landmark outcomes for BSC that were consistent with observed data in the literature and predicted outcomes reported in TA866 and TA405 (7, 55). The use of other distributions are explored in scenario analyses. A scenario is presented where the proportional hazards assumption is relaxed, in which the best fitting independent model (log-normal distribution) is used to extrapolate OS in both arms.

OS in the economic model is capped by general population mortality sourced from ONS England and Wales life tables (137), ensuring that the per-cycle risk of mortality does not fall below that of the general population. However, due to the poor survival of patients with mCRC, this does not come into effect during the time horizon of the model.

Table 32: OS landmark estimates by parametric distribution, fruquintinib (joint models), pooled data

Distribution	1-year OS	2-year OS	5-year OS	Median (months)
Observed data (KM)	[redacted]	[redacted]	–	8.0
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

†10.4% at 23 months
Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Table 33: OS landmark estimates by parametric distribution, BSC (joint models), pooled data

Distribution	1-year OS	2-year OS	5-year OS	Median (months)
Observed data (KM)	[redacted]	–	–	5.5
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
TA405 model result†	–	4.1%	0.6%	5.3
TA866 model result‡	18.0%	–	0.1%†	5.5†

†Using a stratified log-logistic model
‡Using a generalised gamma joint model
Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival.

As discussed in Section B.2.9.1, in the absence of direct head-to-head evidence comparing the efficacy of fruquintinib with regorafenib or trifluridine-tipiracil, an NMA was conducted to inform relative efficacy for these comparators in the model.

For regorafenib and trifluridine-tipiracil, HRs from the NMA were applied to the extrapolated fruquintinib base case OS curve (regorafenib vs fruquintinib HR: 1.08 [95% CrI: 0.86, 1.33]; trifluridine-tipiracil vs fruquintinib HR: 1.05 [95% CrI: 0.87,1.28]). To validate the estimated outcomes, predicted median survival estimates for regorafenib and trifluridine-tipiracil were compared, and considered consistent, with the observed data reported in the literature from the respective clinical trials (as discussed in Section B.3.1), the predicted outcomes in

TA405 and TA866 ((7, 55)) and RWE identified by the clinical SLR (Appendix D (section D.2.4) (Table 34).

Table 34: Median OS comparisons, regorafenib and trifluridine-tipiracil

Distribution	Median (months)	5-year OS
Regorafenib		
Predicted by economic model (i.e. NMA HR applied to the base case BSC curve)	[redacted]	[redacted]
TA866 model predicted value (7)	7.1	0.4%
Pooled CORRECT and CONCUR (10, 102)	6.9	0.0%
REBECCA RWE study (144)	5.6	–
CORRELATE RWE study (41)	7.7	–
RECORA RWE study (45)	5.8	–
Trifluridine-tipiracil		
Predicted by economic model (i.e. NMA HR applied to the base case BSC curve)	[redacted]	[redacted]
TA405 model predicted value (55)TA405 model predicted value (55)	7.4	1.4%
Pooled RECOURSE and TERRA (7, 9, 109)	7.3	–
Tong RWE study (145)	5.8	–
Stavraka RWE study (62)	7.6	–

Abbreviations: BSC, best supportive care; HR, hazard ratio; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival; RWE, real world evidence.

The resulting OS curves for all treatments are presented in Figure 36.

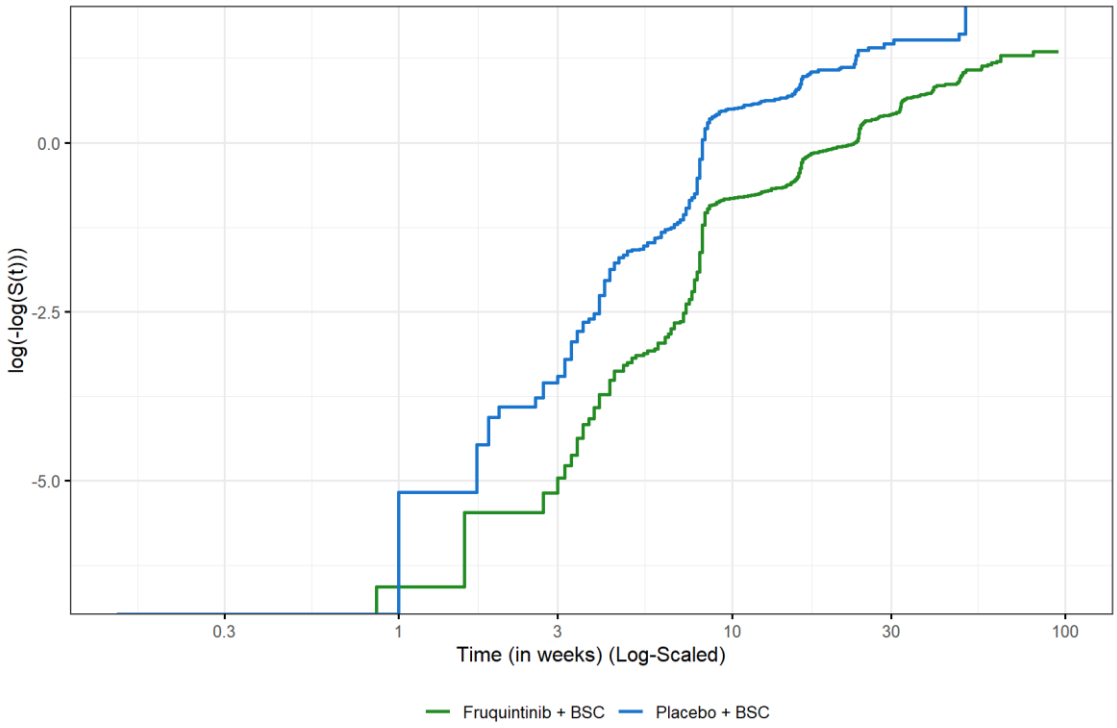
Figure 36: Base case OS curves

†The regorafenib and trifluridine/tipiracil curves are very similar and therefore both curves are not visible.
Abbreviations: BSC, best supportive care; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival.

B.3.3.2.2 Progression-free survival

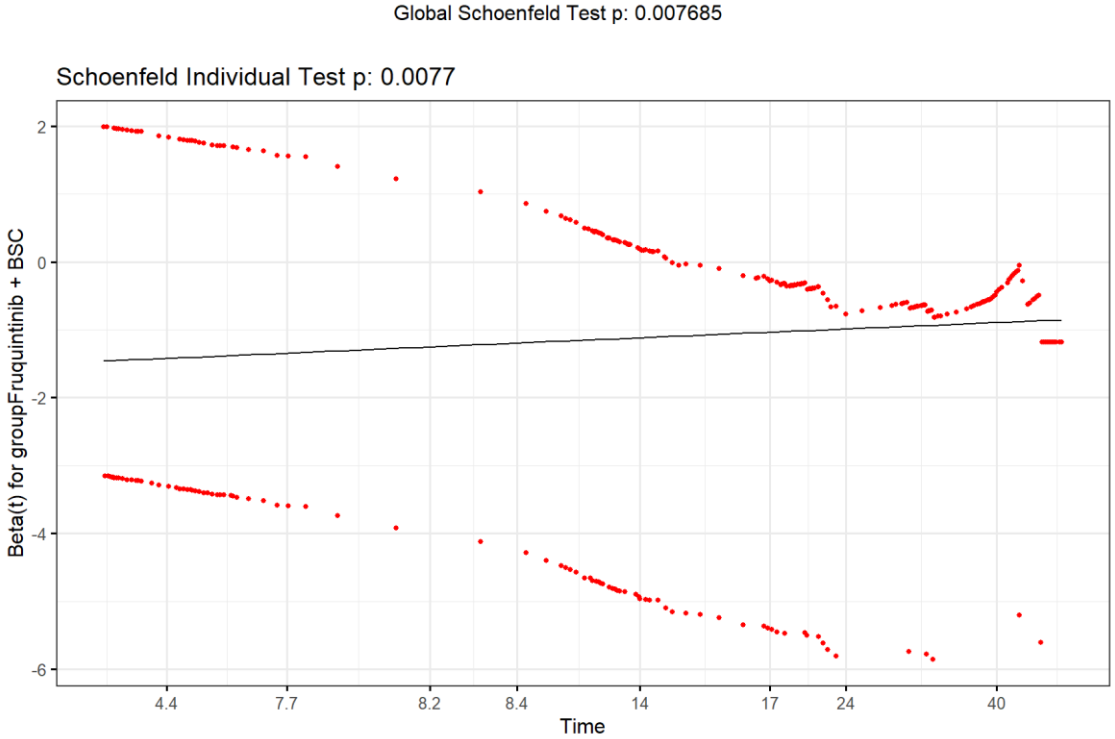
Figure 37 presents the log-cumulative hazard plot for fruquintinib and BSC. The plot is relatively parallel throughout and the curves only cross at the start suggesting that there is no violation of the PH assumption. Similarly, Figure 32 presents the quantile-quantile plot for PFS, with the points clustered around the parallel line throughout, suggesting the AFT assumption may be appropriate. Therefore, the assumption of a constant treatment effect was considered to be appropriate in the base case, and PFS data for fruquintinib and BSC were extrapolated using joint parametric models assuming baseline risks estimated from the BSC arm with a covariate for treatment with fruquintinib, as per the approach for OS (Section B.3.3.2.1). As with OS, the proportional hazards assumption was validated by clinicians at a UK market access advisory board (1st December 2023), who stated that they expected the PH assumption to hold for all model comparators. The global test of the PH assumption provided a p-value less than 0.05, meaning that the null hypothesis of PH was rejected at the 95% level of confidence (Figure 38), and the smoothed hazard plots may suggest that there are differing hazard shapes over time. Therefore, a scenario is presented where PFS for fruquintinib and BSC were extrapolated using independent parametric models.

Figure 37: Log cumulative hazard plot, PFS, pooled data



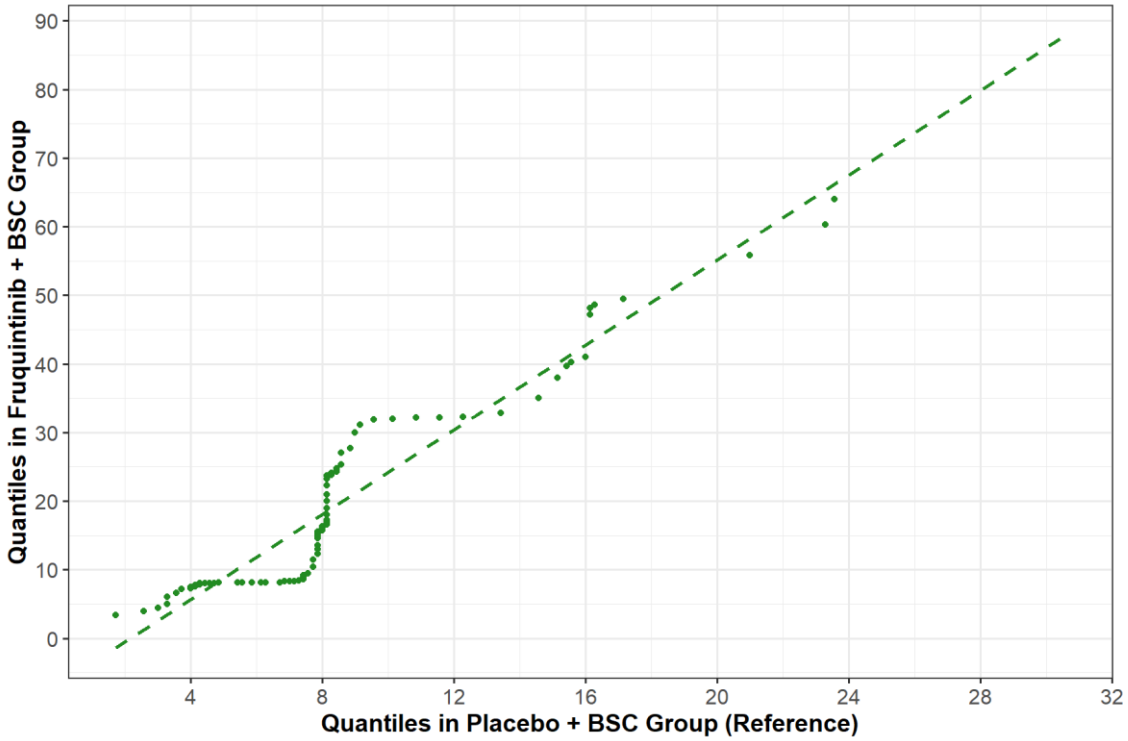
Abbreviations: BSC, best supportive care; PFS, progression-free survival.

Figure 38: Schoenfeld residual plot, PFS, pooled data



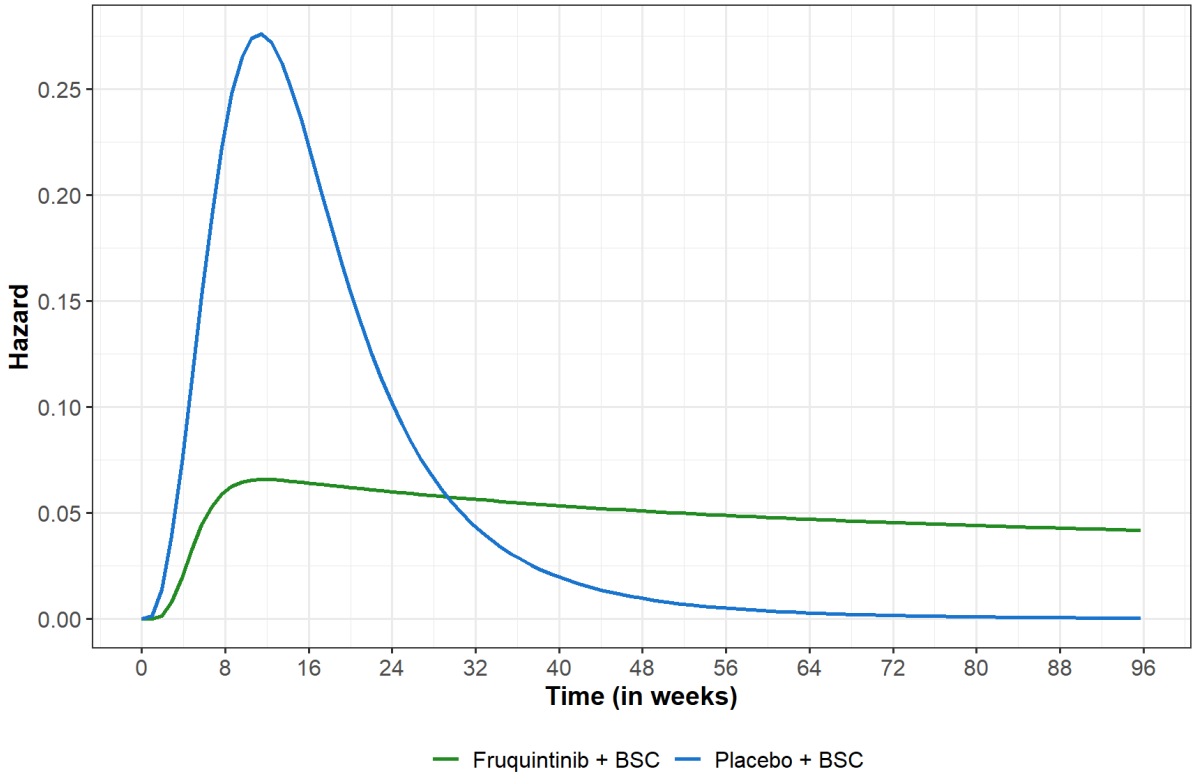
Abbreviations: BSC, best supportive care; PFS, progression-free survival.

Figure 39: Quantile-quantile plot, PFS, pooled data



Abbreviations: BSC, best supportive care; PFS, progression-free survival.

Figure 40: Smoothed hazard plot, PFS, pooled data



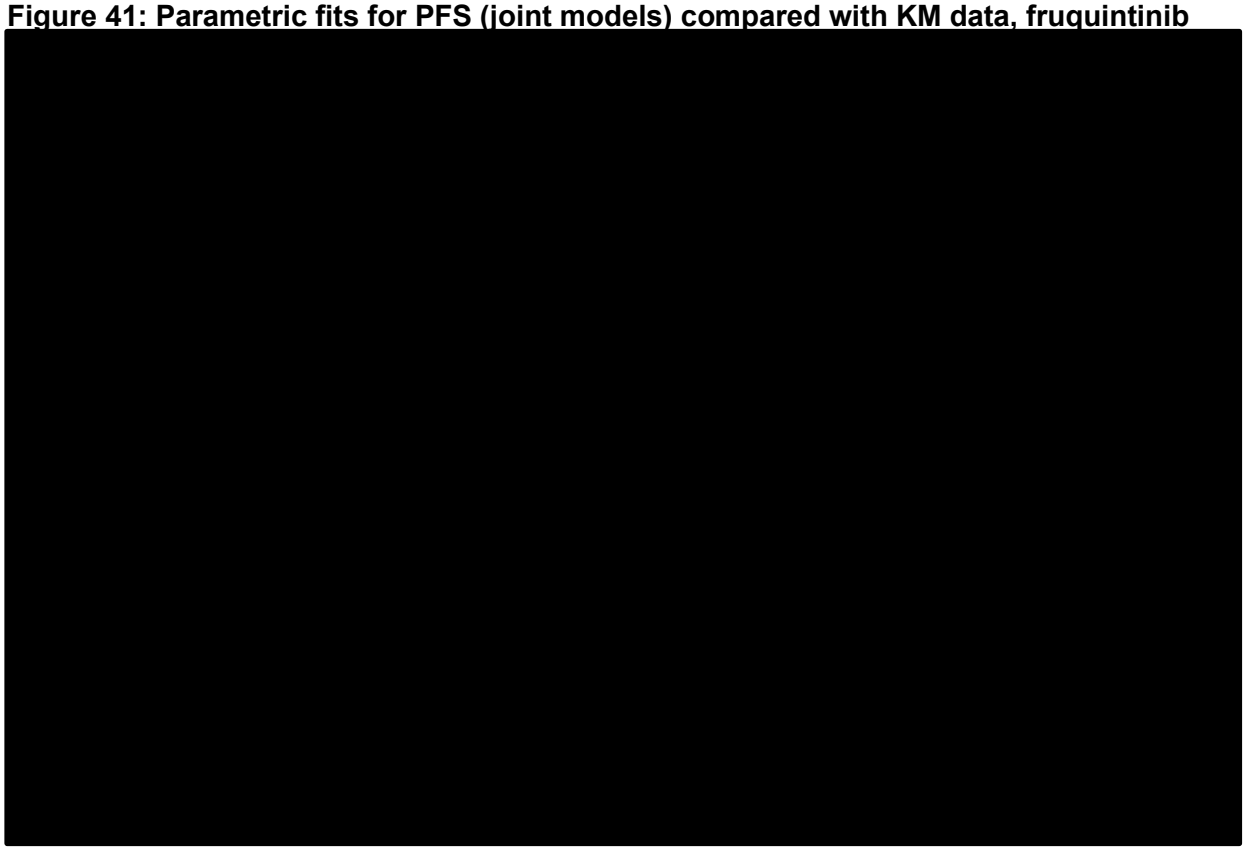
Abbreviations: BSC, best supportive care; PFS, progression-free survival.

Figure 41 and Figure 42 present plots of the PFS parametric distributions and KM curves for fruquintinib and BSC, respectively. Similar to OS, PFS KM data for fruquintinib and BSC

were mature at data cut-off, with 85% and 92% of patients having experienced a PFS event at maximum follow-up (22.1 months) in the fruquintinib and BSC arms, respectively. The log-logistic, log-normal, and generalised gamma curves were associated with the best statistical fit based on minimisation of AIC and BIC of the seven parametric curves that were fitted (Table 35).

On visual inspection, for fruquintinib, all curves appear to have little difference between them. However, the exponential distribution does not appear to provide a good fit to the observed data, and appears to overpredict PFS, from 6 months, and particularly at 12 months ([redacted]% vs [redacted]% for the exponential curve and the KM, respectively). The Gompertz, gamma and Weibull curves appear to overpredict PFS at approximately 6 months vs the observed data ([redacted], [redacted] and [redacted] PFS vs 24.8% in the observed data). The log-logistic, log-normal, and generalised gamma curves provide plausible PFS estimates vs the observed data at all time points and predict observed median PFS well (Table 36). For BSC, the gamma and Weibull curves match the observed data most closely, with the remaining distributions overpredicting PFS at around 6 months. All curves appear to have little difference between them with respect to visual fit.

Figure 41: Parametric fits for PFS (joint models) compared with KM data, fruquintinib



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Figure 42: Parametric fits for PFS (joint models) compared with KM data, BSC

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival.

Table 35: PFS goodness-of-fit statistics for fruquintinib and BSC (joint models), pooled data

Distribution	Fruquintinib and BSC	
	AIC	BIC
Exponential	7296.2	7306.2
Weibull	7040.6	7055.6
Gompertz	7249.0	7264.0
Log-logistic	6864.9	6879.9
Log-normal	6866.7	6881.7
Gamma	6949.1	6964.2
Generalised gamma	6867.4	6887.4

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival.

Landmark estimates of PFS for each distribution and the observed data for fruquintinib and BSC are presented in Table 36 and Table 37, respectively. Most of the curves predict similar 1 and 2-year PFS for fruquintinib and BSC due to the maturity of the FRESCO and FRESCO-2 data. Clinical expert opinion elicited during the UK market access advisory board (1st December 2023) advised that 0% of patients in either treatment arm are expected to be progression-free at 2 years. This is consistent with the PFS landmark estimates predicted by the Weibull, Gompertz, log-normal, gamma and generalised gamma distributions.

Median estimates for each BSC curve were also compared with reported medians from relevant RCTs and modelled outcomes , based on committee preferred assumptions, reported in TA405 and TA866 (7, 9, 10, 55, 102, 109). The reported median PFS in relevant RCTs for BSC ranged from 1.7 months (CONCUR, CORRECT, RECOURSE) to 1.8 months (TERRA) (7, 9, 10, 55, 102, 109). These results are consistent with the predictions of median PFS with the Weibull, log-logistic, log-normal, gamma and generalised gamma distributions. Median and landmark estimates of PFS for BSC from TA405 and TA866 are most consistent with the predicted PFS estimates for the generalised gamma and log-normal distributions (Table 37).

A joint model with a log-normal distribution was hence chosen for the base case extrapolation as it provided a good statistical and visual fit to the observed fruquintinib and BSC data, provided clinically plausible long-term estimates of PFS, as per clinical opinion, and provided predicted median and landmark outcomes for BSC that were consistent with observed data in the literature and predicted outcomes reported in TA866 and TA405. All other distributions are presented in scenario analyses. A scenario analysis is presented that where the best-fitting independent models in each arm (log-normal) were chosen. In the model, PFS is capped by the OS curve to prevent implausible model outcomes.

Table 36: PFS landmark estimates by parametric distribution, fruquintinib (joint models), pooled data

Distribution	6-month PFS	1-year PFS	2-year PFS	5-year PFS	Median (months)
Observed data (KM)	[redacted]	[redacted]	–	–	3.7
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 37: PFS landmark estimates by parametric distribution, BSC (joint models), pooled data

Distribution	6-month PFS	1-year PFS	2-year PFS	Median (months)
Observed data (KM)	[redacted]	–	–	1.6
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
TA405 (55)†	–	–	–	1.7
TA866 (7)‡	–	0.2%	–	–

†Using a stratified log-logistic model. ‡Using KM followed by exponential distribution (committee preferred using the KM directly).
Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival.

For regorafenib and trifluridine-tipiracil, HRs from the NMA were applied to the extrapolated fruquintinib base case PFS curve (regorafenib vs fruquintinib HR: 1.52 [95% CrI: 1.23, 1.85]; trifluridine-tipiracil vs fruquintinib HR: 1.49 [95% CrI: 1.25, 1.82]). Predicted median PFS estimates were estimated to be slightly longer than the pooled data from CORRECT and CONCUR for regorafenib and RECOURSE and Yoshino for trifluridine-tipiracil, but importantly, were aligned with the predicted outcomes in TA866 and TA405 (7, 55) and RWE identified by the clinical SLR (Appendix D, section D.2.4) (Table 34).

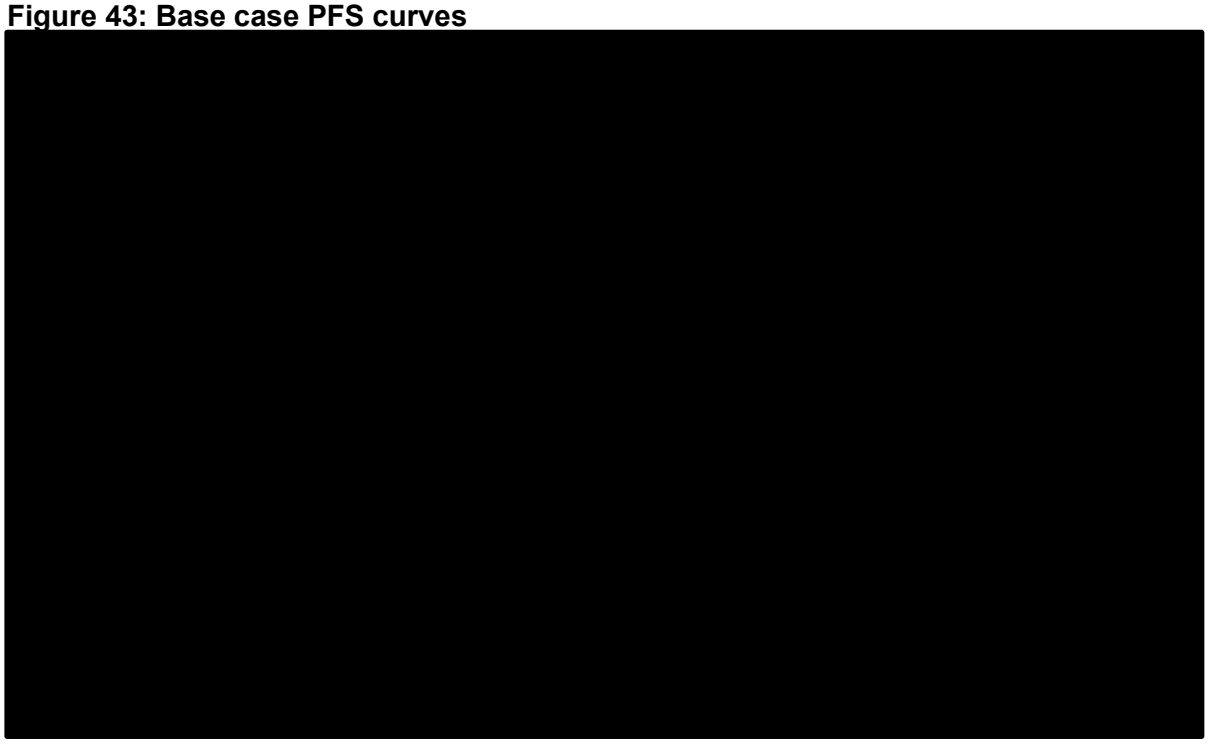
Table 38: Median PFS comparisons, regorafenib and trifluridine-tipiracil

Distribution	Median (months)	1-year PFS
Regorafenib		
Predicted by economic model (NMA HR applied to the base case fruquintinib curve)	[redacted]	[redacted]
TA866 model predicted value (7)	2.8	1.5%
Pooled CORRECT and CONCUR (10, 102)	2.1	4.7%
REBECCA RWE study (144)	2.7	7.0%
CORRELATE RWE study (41)	2.9	–
RECORA RWE study (45)	3.1	–
Trifluridine-tipiracil		
Predicted by economic model (NMA HR applied to the base case fruquintinib curve)	[redacted]	[redacted]
TA405 model predicted value (55)TA405 model predicted value (55)	2.9	–
Pooled RECOURSE and Yoshino (9, 55, 109)	1.9	–
Tong RWE study (145)	3.2	–
Stavraka RWE study (62)	3.3	–

Abbreviations: BSC, best supportive care; HR, hazard ratio; KM, Kaplan-Meier; NMA, network meta-analysis; PFS, progression-free survival; RWE, real-world evidence.

The resulting PFS curves for all model comparators are presented in Figure 43.

Figure 43: Base case PFS curves



†The regorafenib and trifluridine/tipiracil curves are very similar and therefore not both curves are visible.
Abbreviations: BSC, best supportive care; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival.

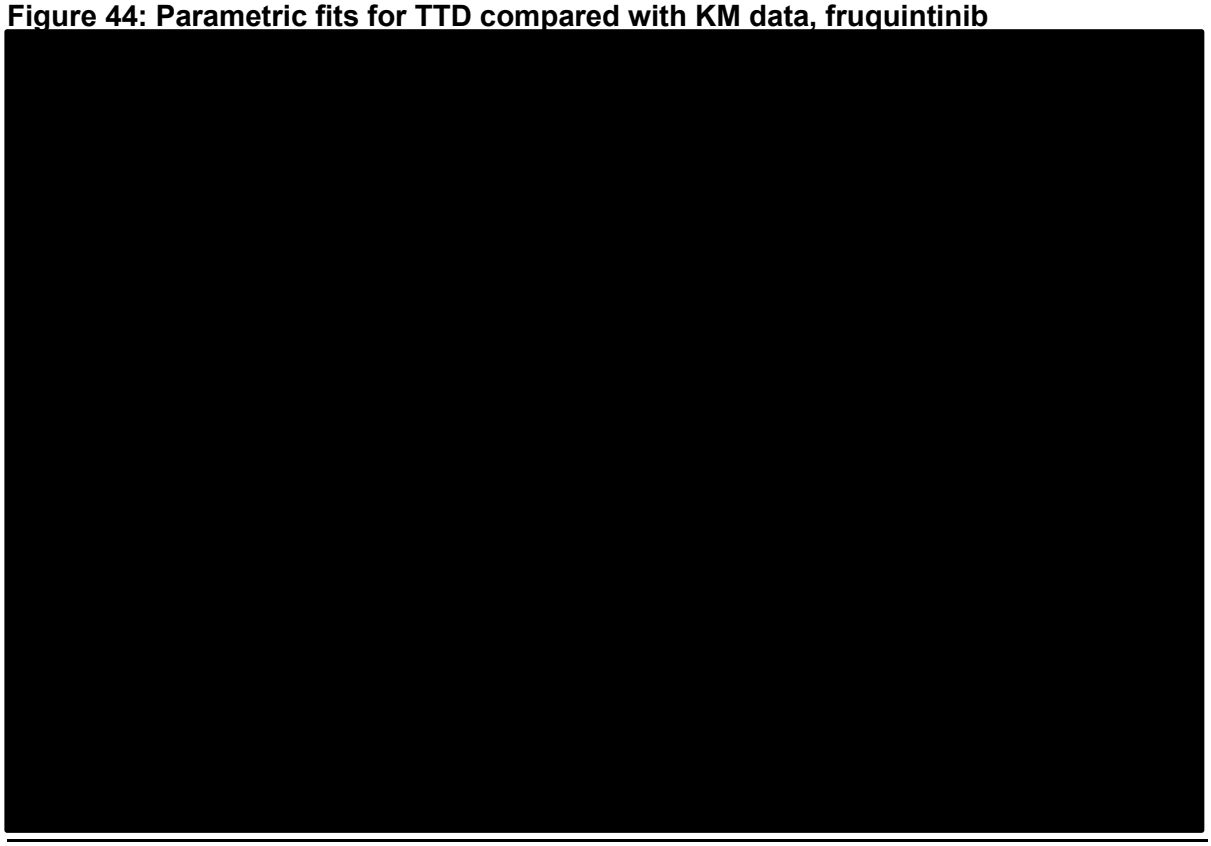
B.3.3.2.3 Time-to-treatment discontinuation

As per the FRESCO and FRESCO-2 trial protocols, patients receiving fruquintinib in the model are treated until disease progression or until unacceptable toxicity occurs (88, 146). Therefore, as AEs can lead to treatment discontinuations, treatment duration was modelled separately to PFS. Clinical expert opinion elicited at the UK market access advisory board (1st December 2023) advised that treatment beyond progression would not happen in UK clinical practice and, as a result, the TTD curve was capped by PFS (11). TTD was defined as the last dose date of the study drug minus the first dose date of the study drug.

Parametric distributions were fit to the TTD KM data for fruquintinib, which were subsequently used to determine treatment acquisition costs over time. Given TTD curves were not required for BSC, an independent model was fit to the fruquintinib TTD data only (Figure 44). Although patients are expected to discontinue treatment early if they experience toxicity or tolerability issues, progression is the cause of discontinuation in many patients, and so alignment between TTD and PFS was considered in choosing the base case distribution. Pooled TTD KM data were highly mature with 94% of patients having discontinued at the end of follow-up in the fruquintinib arm. The log-logistic, generalised gamma and log-normal curves provided the best statistical fit to the KM data based on AIC

and BIC statistics (Table 39). All parametric distributions provided a good visual fit to the observed KM data and provided predictions of median TTD that aligned closely with the observed data. UK clinical experts at the UK market access advisory board (1st December 2023) expected a median TTD of approximately 2.5 months (47). As a result, the log-normal distribution was chosen to extrapolate TTD in the base case. This provided good statistical and visual fit to the KM data, and a median TTD ([redacted] months) most consistent with clinical opinion, and also aligns with the base case distribution selected for PFS. The extrapolated TTD curves sit above the PFS extrapolation beyond one-year, therefore the one-year and two-year estimates of the proportion of patients on treatment is equal to the proportion of patients who are progression-free (Section B.3.3.2.2) when capped by PFS.

Figure 44: Parametric fits for TTD compared with KM data, fruquintinib



Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Table 39: TTD goodness-of-fit statistics for fruquintinib (joint models), pooled data

Distribution	Fruquintinib	
	AIC	BIC
Exponential	5465.0	5469.6
Weibull	5438.5	5447.7
Gompertz	5466.0	5475.2
Log-logistic	5398.5	5407.7
Log-normal	5418.1	5427.3
Gamma	5422.8	5432.0
Generalised gamma	5400.8	5414.6

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation.

Table 40: TTD landmark estimates by parametric distribution, fruquintinib (joint models), pooled data

Distribution	6-month TTD	1-year TTD	2-year TTD	Median (months)
Observed data (KM)	[redacted]	[redacted]	–	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

For TTD, an NMA could not be performed due to a lack of publicly available TTD data for regorafenib and trifluridine-tipiracil. Therefore, TTD for regorafenib and trifluridine-tipiracil were estimated by applying the relevant PFS HRs vs fruquintinib (HR: 1.52 [95% CrI: 1.23, 1.85] and HR: 1.49 [95% CrI: 1.25, 1.82], respectively; Section B.2.9.5.2) to the fruquintinib TTD curve. This assumption was considered appropriate given i) the treatment discontinuation rules previously described, ii) this aligns with the approach taken to estimate comparator time on treatment in TA866, and iii) the similarity in PFS and TTD outcomes observed in the FRESCO and FRESCO-2 data (Section B.3.3.2.2), as well as the CORRECT and RECOURSE trials, and RWE studies identified in the clinical SLR (Appendix D [Section D.2.4, Table 41]). Clinical and health economics experts at the UK market access advisory board (1st December 2023) (47) agreed that this approach was the most appropriate given the available data, and estimated that median TTD would be 2–2.8 months for regorafenib and 1–1.5 months for trifluridine-tipiracil in clinical practice, further validating modelled estimates (Table 41). The base case TTD curves are presented in Figure 45.

Table 41: Median TTD comparisons, regorafenib and trifluridine-tipiracil

Distribution	Median TTD (months)	Median PFS (months)
Regorafenib		
Predicted by economic model (i.e. PFS HR vs fruquintinib TTD)	[redacted]	[redacted]
CORRECT trial (10)	2.8	1.9
REBECCA RWE study (144)	2.2	2.7
CORRELATE RWE study (41)	2.5	2.9
Clinical opinion	2–2.8	–
Trifluridine-tipiracil		
Predicted by economic model (i.e. PFS HR vs fruquintinib TTD)	[redacted]	[redacted]
RECOURSE trial (9)	1.5	2.0
Tong RWE study (145)	3	3.2
Stavraka RWE study (62)	3	3.3
Clinical opinion	1–1.5	–

Abbreviations: HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; RWE, real world evidence; TTD, time to treatment discontinuation.

Figure 45: Base case extrapolations, TTD

Abbreviations: KM, Kaplan Meier; TTD, time-to-treatment discontinuation.

B.3.4 Adverse reactions

As highlighted in Section B.2.10.1, fruquintinib was generally well tolerated, with fewer toxicities than comparator treatments. The model considers Grade 1 or 2 treatment-related TEAEs that occurred in at least 10% of patients, and Grade 3 or above treatment-related TEAEs that occurred in at least 2% of patients across any modelled treatment. Grade 1 and 2 adverse events were included in line with the Committee's preferred approach in TA866 (53).

The proportion of patients experiencing AEs associated with fruquintinib and BSC in the model are informed by the pooled data from FRESCO and FRESCO-2. Treatment-related TEAEs for trifluridine-tipiracil and regorafenib were sourced from TA866 (7); proportions were based on pooled data from CONCUR and CORRECT for regorafenib, and RECOURSE, TERRA and Yoshino, 2012 for trifluridine-tipiracil. The proportion of patients experiencing Grade 3 or above treatment-related TEAEs is presented in Table 42. The proportion of patients experiencing Grade 1–2 treatment-related TEAEs is presented in Table 9, Appendix N. These TEAEs are applied as a one-off cost and QALY loss in the first cycle of the model. Grade 1–2 adverse events were not reported in the trial publications for regorafenib and trifluridine-tipiracil, therefore incidences are calculated using the difference between all treatment-related TEAEs and Grade 3 or above treatment-related TEAEs reported in the trial publications, as per the Committee's preferred approach in TA866. The proportion of AEs in comparator trials were pooled and reweighted based on trial population size (9, 10, 102, 104, 109). Clinicians at the UK market access advisory board (1st December 2023) agreed that there were no further adverse events that would be of concern for patients with mCRC and that all important AEs were captured in the model.

Table 42: Grade ≥3 treatment-related TEAEs reported in ≥2% of patients in any treatment arm, as applied in the model

Adverse event	Fruquintinib N=734 n (%)	BSC N=367 n (%)	Trifluridine-tipiracil N=917 n (%)	Regorafenib N=636 n (%)
Anaemia	1 (0.1)	4 (1.1)	163 (17.8)	14 (2.2)
Asthenia	24 (3.3)	3 (0.8)	18 (2.0)	NR
Diarrhoea	23 (3.1)	0	23 (2.5)	36 (5.7)
Fatigue	18 (2.5)	1 (0.3)	28 (3.0)	52 (8.2)
Hand-foot syndrome	58 (7.9)	0	NR†	105 (16.5)
Hypertension	109 (14.9)	5 (1.4)	NR†	51 (8.0)
Aspartate aminotransferase increased	3 (0.4)	2 (0.5)	33 (3.6)	8 (1.3)
Hyperbilirubinaemia	1 (0.1)	2 (0.5)	64 (7.0)	19 (3.0)
Leukopenia	1 (0.1)	0	201 (21.9)	3 (0.5)
Neutropenia	0	1 (0.3)	347 (37.8)	3 (0.5)
Rash	0	0	NR†	35 (5.5)
Thrombocytopenia	3 (0.4)	1 (0.3)	40 (4.4)	18 (2.8)
Lymphopenia	0	0	50 (5.5)	NR†
Proteinuria	16 (2.2)	1 (0.3)	NR†	NR†
Anorexia	NR	NR	5 (0.5)	16 (2.5)
Decreased appetite	9 (1.2)	2 (0.5)	19 (2.1)	NR†
Febrile neutropenia	NR†	NR†	25 (2.8)	3 (0.5)
Mucositis	NR†	NR†	NR†	15 (2.4)
Hypophosphataemia	NR†	NR†	42 (4.6)	28 (4.4)
Lipase level increased	1 (0.1)	0	NR†	22 (3.5)
Source	FRESCO and FRESCO-2 pooled data (116)		TA866 committee papers (7)	

†Where AE data were not reported the value was assumed to be zero.
Abbreviations: BSC, best supportive care; NR, not reported; TEAE, treatment-emergent adverse event.

B.3.5 Measurement and valuation of health effects

B.3.5.1 Health-related quality-of-life data from clinical trials

Health-related quality of life (HRQoL) was measured in FRESCO-2 only. Although no HRQoL data were captured in FRESCO, FRESCO-2 is a global Phase III RCT in the population of interest, representing a large patient population (N=691). Patient-reported HRQoL data were collected using EORTC QLQ-C30 and EQ-5D-5L questionnaires administered:

- At screening
- On Day 1 of treatment cycles 2, 3, 4, and beyond up to Cycle 20
- At the end of treatment (30±3 days after last dose of therapy).

Table 43 shows the incidence of missing EQ-5D-5L data at each visit. Generally, the compliance rate was high. Baseline EQ-5D-5L data were missing for 4.3% and 8.7% patients in the placebo and fruquintinib arms, respectively. The rate of missing data was similar between the two arms and ranged from 6.3–12.7% and 2.8–13.7% in the placebo and fruquintinib arms, respectively, at visits where the number of patients remaining was greater than 10[4]. There were few available EQ-5D-5L data beyond Cycle 6, with fewer than 10 patients remaining by Cycle 6 and Cycle 13 in the BSC and fruquintinib arms, respectively.

Table 43: Summary of EQ-5D-5L questionnaire – missing data, ITT population

Visit	Placebo + BSC (N=230) n (%)†	Fruquintinib + BSC (N=461) n (%)†
Baseline	10/230 (4.3)	40/461 (8.7)
Cycle 2	15/169 (8.9)	37/400 (9.3)
Cycle 3	8/63 (12.7)	26/280 (9.3)
Cycle 4	4/34 (11.8)	22/223 (9.9)
Cycle 5	1/16 (6.3)	22/161 (13.7)
Cycle 6	0/8	10/138 (7.2)
Cycle 7	0/2	11/95 (11.6)
Cycle 8	0/2	8/74 (10.8)
Cycle 9	0/1	4/47 (8.5)
Cycle 10	0/1	1/36 (2.8)
Cycle 11	0/1	1/22 (4.5)
Cycle 12	1/1 (100)	0/16
Cycle 13	0/1	0/8
Cycle 14	0	0/6
Cycle 15	0	1/6 (16.7)
Cycle 16	0	0/4
Cycle 17	0	0/4
Cycle 18	0	0/4
Cycle 19	0	0/1
Cycle 20	0	0/1
Overall post-baseline	34/228 (14.9)	35/458 (7.6)

†Percentages are based on the number of subjects in each treatment group unless otherwise specified.
Abbreviations: BSC, best supportive care; ITT, intention-to-treat.

B.3.5.2 Mapping

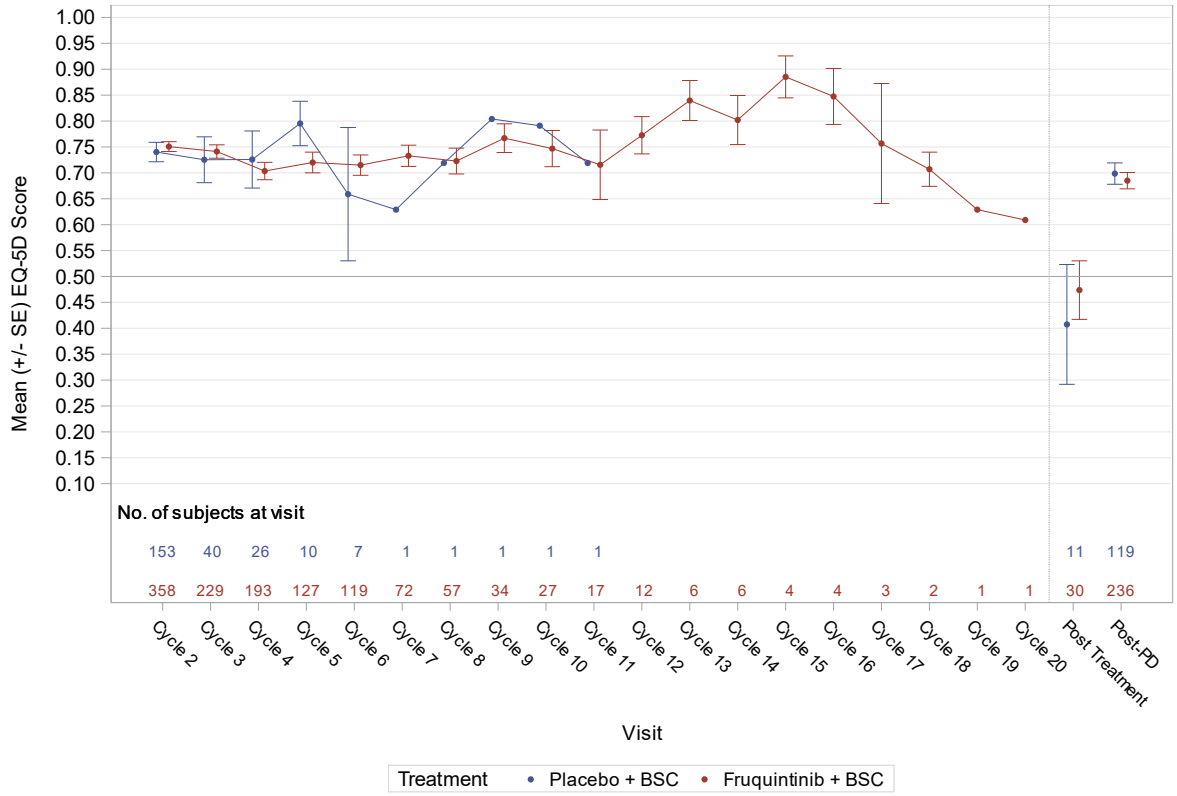
EQ-5D-5L data collected in FRESCO-2 were mapped to EuroQol five-dimension three-level (EQ-5D-3L) using the function developed by the NICE DSU using the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) dataset, and published by Hernández-Alava et al (147), as recommended in the NICE methods guide (138).

[4] A threshold of 10 patients was arbitrarily considered as a sufficient number such that the extent of missing data can be reasonably assessed.

The estimated mean EQ-5D-3L score at baseline was 0.767 (SD, 0.179) and 0.753 (SD, 0.178) in the fruquintinib and placebo arms, respectively. The mean overall EQ-5D-3L utility score at baseline was 0.763 (SD, 0.179); this value was considered the best estimate for the population average and was applied when centring the baseline EQ-5D-3L utility scores for adjustments in the regression models (Section B.3.5.5).

Figure 46 presents the mean UK EQ-5D-3L scores per visit. The mean and median utility values were similar for fruquintinib and placebo at baseline and up to Cycle 5, where both arms had at least 10 patients per visit.

Figure 46: Mean EQ-5D-3L score by visit



Abbreviations: BSC, best supportive care; EQ-5D-3L, EuroQol five-dimension three-level; SE, standard error.

B.3.5.3 Health-related quality-of-life studies

An SLR was conducted on 23rd October 2023 to identify utility data in mCRC in patients who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (anti-VEGF) therapy, and, if *RAS* wild type, an anti-epidermal growth factor receptor (anti-EGFR) therapy. Full details of the search strategy, results and summary characteristics for all included studies are provided in Appendix H.

Of the 21 included studies in the SLR, 10 (7, 55, 135, 148-154) met the NICE reference case requirements for health state utility value (HSUV) evidence, in that they reported utility values derived from a representative UK population or using UK tariffs, and were elicited using a preference-based measure, such as time trade-off (TTO) or standard gamble, and an appropriate method for valuing health states: six were primary utility studies (148-150, 152-154) and four were prior HTAs (7, 55, 135, 151) (Table 44).

Of the six primary utility studies (148-150, 152-154), three studies provided treatment-independent utility values (Table 44) (148, 149, 153). Pre-progression utility values ranged from 0.74 to 0.82, with post-progression values of 0.64 for palliative patients and 0.73 for patients receiving subsequent lines of therapy or BSC. The remaining three studies reported treatment-specific utilities (Table 44) (150, 152, 154): data from Siena et al. (2013) were the most relevant to the current decision problem with pre-progression utility values of 0.67 for regorafenib (152). A detailed description of the six primary utility studies is provided in Appendix H.

In the NICE appraisal TA405 (trifluridine-tipiracil) (55), due to the absence of HRQoL data from Yoshino et al. 2012 (110) and RECOURSE RCT (9), and limited HRQoL studies meeting NICE reference case criteria, the company base case analysis used an average of health state utility values from CORRECT (10) and a prior appraisal assessing cetuximab for the first-line treatment of mCRC (TA176 (155)). The external assessment group (EAG) and the committee found pooling values from CORRECT (10) and TA176 (155) methodologically inferior to using CORRECT alone, citing the derivation of utilities using a non-reference case instrument (HUI3) and earlier line population as its rationale. In addition, the post-progression utility values were derived from individuals with *KRAS* wild-type mCRC refractory to chemotherapy, and the source of these data was not clear (55). The AE disutility associated with treatment with trifluridine-tipiracil was assumed to be 0.01 based on the difference between the utility scores 0.73 (pre-progression on treatment) and 0.74 (pre-progression BSC) (55). In the SMC submission (135), utility values were derived from the CORRECT study. The approach to disutilities was not reported in the SMC report (135), but was likely as reported for the NICE TA405 (7).

In the regorafenib appraisal (TA866) (7), utility values were derived from pooled EQ-5D-3L data from the CORRECT and CONCUR trials. Despite differences in EQ-5D-3L data between regorafenib and BSC, the model assumed no treatment-dependent utilities (7). Concerns were raised by the EAG about the use of pooled end-of-treatment results to determine the post-progression utility value (7). The committee observed a significant contrast between pre- and post-progression utility values 0.72 and 0.59, respectively.

Clinical professionals elaborated on the challenges of managing disease progression while on best supportive care, highlighting its impact on quality of life (7). AE disutility values in the model, excluding hypertension, were derived from non-small cell lung cancer and breast cancer studies (values reported in Section B.3.5.4 and Appendix H) (7).

In the SMC submission for encorafenib + cetuximab (151) utility values were based on EQ-5D-5L data from the BEACON CRC study. These values were cross-walked to generate EQ-5D-3L values (151). Utilities were defined by progression status and were averaged across the encorafenib plus cetuximab and control arm of the BEACON RCT (151). The decision to pool utilities was reported to have been informed by clinical expert feedback suggesting that progression status would be the main driver of quality of life (151). Treatment-specific utilities were therefore not explored in the analysis. The mean pre-progression utility 0.743 and the post-progression utility was 0.627 (151). No quality-of-life decrements were applied to adverse events, assuming that the EQ-5D data already incorporated their effects (151).

The studies identified by the SLR were used to validate utility values estimated by the regression models (Section B.3.5.5).

Table 44: Overview of utility values (NICE reference case) from the literature

Source	Population of mCRC	Country	Instrument + valuation	Pre progression mean utility values	Post progression mean utility values	Disutilities
Primary utility studies						
Farkkila 2013 (148)	All lines (29.7% with advanced disease)	Finland	EQ-5D UK tariff	Non-palliative (metastatic): 0.82 (0.20) [n=108]	Advanced disease receiving palliative care: 0.64 (SD 0.31) [n=41]	Metastatic cohort: –0.016; palliative care cohort: –0.107
Franken 2020 (149)	mCRC stable disease or better following 6 cycles of initial chemotherapy with CAPOX-B	The Netherlands	EQ-5D-3L UK tariff	Observed utility 0.803 (SD 0.197; −0.239, 1); predicted utility (Longworth et al – UK tariff): 0.810 (SD 0.152; –0.307, 0.955)	–	–
Koukakis 2016 (150)	3rd/4th line RAS wild type mCRC	International including UK	EQ-5D	Panitumumab baseline value: 0.78 (95% CI: – 0.07, 1.00) [n=62]; BSC baseline value 0.73 (95% CI: 0.09, 1.00) [n=60]	–	Disutility values were reported for skin toxicities, grouped by: • two different definitions for toxicities • overall health rating scores by worst skin toxicity grade • treatment group and worst skin toxicity grade Adjusted least square means ranged from –0.048 to 0.175†
Siena 2013 (152)	Adults with mCRC progressing after all standard therapies (who completed the CORRECT trial)	International including UK	EQ-5D	Regorafenib: 0.67 (95% CI 0.64,0.70); Placebo: 0.67 (95% CI: 0.64, 0.70)	–	–
Stein 2014 (153)	All lines + no brain metastases	UK, The Netherlands	EQ-5D-3L UK tariff	0.74 (SD 0.23) [n=42]	0.73 (SD 0.29) [n=33] (progressed during or after second-line therapy and were receiving third or subsequent lines of therapy or BSC)	–
Wang 2011 (154)	Chemorefractory WT KRAS	Worldwide including UK	EQ-5D UK tariff	No toxicity panitumumab 0.77 (SD NR) [n=104); No toxicity BSC 0.66 (SD NR)	Panitumumab 0.63 (SD NR) [n=68]; BSC 0.64 (SD NR) [n=63]	–

Source	Population of mCRC	Country	Instrument + valuation	Pre progression mean utility values	Post progression mean utility values	Disutilities
				[n=103]; Toxicity panitumumab 0.60 (SD NR) [n=37]; Toxicity BSC 0.44 (SD NR) [n=13]		
Prior technology appraisals						
TA866 (7) (used pooled CORRECT + CONCUR RCT(10, 102) utilities)	Adults with previously treated mCRC	Worldwide including UK	EQ-5D-3L UK tariff	Regorafenib (baseline value): 0.716; trifluridine-tipiracil: 0.712; BSC: 0.719	0.59 (0.014)	AE disutility values sourced from Lloyd et al. (2006) (156), Nafees et al. (2008) (157), and Doyle et al.(157), (2008) (158) (values reported in Section B.3.5.4 and Appendix H)
TA405 (55) (Grothey: CORRECT (10))	Adults with previously treated mCRC (26% 1st/2nd line; 26% 3rd line; 48% 4th line)	Worldwide including UK	EQ-5D UK tariff	Regorafenib (baseline value) 0.73 (SD0.25) [n=500]; Placebo (baseline value) 0.74 (SD 0.27) [n=253]	Regorafenib 0.59 (0.31) [n=500]; Placebo 0.59 (SD 0.34) [n=253]	AE disutility for being on trifluridine-tipiracil: 0.01
SMC 1221-17 (trifluridine-tipiracil) (135)	Adults with previously treated mCRC (26% 1st/2nd line; 26% 3rd line; 48% 4th line)	Worldwide including UK	EQ-5D UK tariff	Trifluridine-tipiracil 0.73; BSC 0.74	0.59	NR (assumed to have taken same approach as NICE TA405)
SMC 2312 (encorafenib + cetuximab) (151) (used BEACON utilities)	Adults with mCRC + BRAF V600E who have received prior therapy	Worldwide including UK	EQ-5D-5L UK tariff (assumed for UK HTA submission)	0.743	0.627	NR

†Three separate disutility analyses were carried out using different health state definitions, and not all data are reported here; for a full list of disutility results see Koukakis et al, 2016 (150).
Abbreviations: AE, adverse event; BSC, best supportive care; EQ-5D-3L, EuroQol five-dimension three-level; EQ-5D-5L, EuroQol five-dimension five-level; HTA, health technology assessment; mCRC, metastatic colorectal cancer; NR, not reported; RAS, rat sarcoma virus; SD, standard deviation; TA, technology appraisal; UK, United Kingdom.

B.3.5.4 Adverse event utility decrements

The impact of AEs on patients' HRQoL are likely captured in the utility analysis described in Section B.3.5.5; however according to UK clinical expert opinion, some AEs are difficult to distinguish from the long-term effects of late-stage cancer and can wax and wane during treatment (47), therefore patients may not have been experiencing AEs at the time the EQ-5D-5L was administered in FRESCO-2. Therefore, standalone utility decrements were included in the model to capture the impact of AEs on patients' HRQoL over time. Clinicians also advised that the majority of AEs occur at the beginning of treatment with most resolving within 2-14 days, therefore the impact of treatment-related TEAEs on HRQoL is captured as a one-off QALY decrement applied in the first cycle of the model.

As described in Section B.3.4, Grade ≥3 treatment-related TEAEs occurring in ≥2% of patients, and Grade 1–2 treatment-related TEAEs occurring in ≥10% of patients in any treatment arm were included in the analysis. The AE proportions (Section B.3.4) were combined with an AE duration and a mean AE disutility associated with each treatment-related TEAE to calculate a total QALY loss for each treatment.

Most Grade ≥3 and Grade 1–2 treatment-related TEAEs were assumed to have a 1 week duration as per TA866 (53) and TA405 (44). This is in line with feedback elicited from UK clinicians following the UK market access advisory board (1st December 2023) (11) that most AEs would resolve with 2-14 days (47). Clinicians highlighted that diarrhoea would take longer to resolve (14-28 days), and is therefore assigned a 3-week duration, and decreased appetite likely resolves in 1-7 days, so is therefore assigned a 0.5-week duration as the mid-point of this range. Clinicians also highlighted that most patients would not be aware they have hypertension, therefore hypertension is assumed to have no utility decrement.

The disutilities associated with each Grade ≥3 treatment-related TEAE are presented in Table 45 and were sourced from TA866. All Grade 1–2 treatment-related TEAEs (Table 9, Appendix N) were assigned a disutility of 0.01, as per the committee preferred approach in TA866, and in line with Grade 1–2 AE disutilities reported in the literature (159). However, this is a conservative assumption as most Grade 1–2 treatment-related TEAEs are mild and their inclusion may be double counting as general population utility values may include a proportion of people who experience these milder events. UK clinicians highlighted myelosuppression, fatigue or asthenia, decreased appetite, hand-foot syndrome, and diarrhoea as the most burdensome AEs for patients treated for mCRC, therefore a scenario has been explored where, for these AEs, the disutility for Grade ≥3 AEs were applied to

Grade 1–2 AEs. The average AE utility decrement applied for each treatment is reported in Table 46.

Table 45: Grade ≥3 disutilities per adverse event included in the model

Adverse event	Disutility	Source
Anaemia	0.0900	Assumed equal to Neutropenia Nafees et al, 2008 (157)
Asthenia	0.1150	Lloyd et al, 2006 (156)
Diarrhoea	0.1030	Lloyd et al, 2006 (156)
Fatigue	0.1150	Lloyd et al, 2006 (156)
Hand-foot syndrome/Palmar-plantar erythrodysesthesia	0.0320	Assumed equal to Skin reactions, Nafees et al, 2008 (157)
Hypertension	0.0000	Assumption based on clinical feedback
Aspartate aminotransferase increased	0.0900	Assumed equal to Neutropenia, Nafees et al, 2008 (157)
Blood bilirubin increased	0.0900	Assumed equal to Neutropenia, Nafees et al, 2008 (157)
Leukopenia	0.0900	Assumed equal to Neutropenia, Nafees et al, 2008 (157)
Neutropenia	0.0900	Nafees et al, 2008 (157)
Rash	0.0320	Nafees et al, 2008 (157)
Thrombocytopenia	0.0900	Assumed equal to Neutropenia, Nafees et al, 2008 (157)
Lymphopenia	0.0900	Assumed equal to Neutropenia, Nafees et al, 2008 (157)
Proteinuria	0.0900	Assumed equal to Neutropenia, Nafees et al, 2008 (157)
Anorexia	0.1030	Lloyd et al, 2006 (156)
Decreased appetite	0.1030	Lloyd et al, 2006 (156)
Febrile neutropenia	0.1150	Lloyd et al, 2006 (156)
Mucositis	0.0320	Assumed equal to Skin reactions, Nafees et al, 2008 (157)
Hypophosphataemia	0.0900	Assumed equal to Neutropenia, Nafees et al, 2008 (157)
Lipase level increased	0.0900	Assumed equal to Neutropenia, Nafees et al, 2008 (157)

Abbreviations: AE, adverse event.

Table 46: Total AE QALY decrement per treatment applied in the model

Treatment	Total AE QALY decrement
Fruquintinib	0.0009
Regorafenib	0.0015
Trifluridine-tipiracil	0.0030
BSC	0.0003

Abbreviations: AE, adverse event; BSC, best supportive care; QALY, quality-adjusted life year.

B.3.5.5 Health-related quality-of-life data used in the cost-effectiveness analysis

EQ-5D-3L utility scores derived from FRESCO-2 were analysed using mixed-effects repeated-measures linear regression models for ITT patients with available baseline and at least one post-baseline EQ-5D-3L value (aligning with the patient-reported outcomes analysis presented in Section B.2.6.2.3). A total of 641 (92.8%) out of 691 ITT patients in FRESCO-2 had a non-missing baseline value, with 2476 total observations (Table 47). 585 (84.7%) patients had at least one post-baseline value and 544 (78.7%) had both a baseline and a post-baseline value and were included in the utility analysis population.

Table 47: Patients included in utility analysis

	Fruquintinib + BSC (N=461)	Placebo + BSC (N=230)	Overall (N=871)
No. of patients with baseline or post-baseline value, n (%)	453 (98.3)	229 (99.6)	682 (98.7)
No. of patients with non-missing baseline value, n (%)	421 (91.3)	220 (95.7)	641 (92.8)
No. of patients with at least one non-missing post-baseline value, n (%)	404 (87.6)	181 (78.7)	585 (84.7)
No. of patients with non-missing baseline value and at least one non-missing post-baseline value, n (%)	372 (80.7)	172 (74.8)	544 (78.7)
No. of non-safety patients, n (%)	1 (0.2)	2 (0.9)	3 (0.3)

Abbreviations: BSC, best supportive care.

A random intercept for each patient was included in the models to account for the clustering of multiple observations. In addition, the models were adjusted for baseline utility that was centred at the mean value of the overall eligible population as a continuous fixed effect to consider differences in baseline utility at randomisation.

Univariate analyses were conducted to identify relevant covariates for inclusion in the multivariable mixed-effects repeated-measures linear regression models. Based on literature on HRQoL predictors in mCRC (153), the following univariate models were fitted: baseline age, sex (female vs male), baseline utility, treatment (fruquintinib vs placebo), prior treatment (prior trifluridine-tipiracil or regorafenib vs both), progression status (progression-free vs progressed), ongoing Grade ≥3 TEAE (yes vs no), and death within 28 days of EQ-5D visit (yes vs no). Clinical experts at the UK market access advisory board (1st December 2023) (47) confirmed that the main drivers of HRQoL in mCRC had been captured in the analysis.

These univariate analyses indicated that progression status, ongoing Grade ≥3 TEAE, and proximity to death were significant predictors of utility and were therefore the only

covariables included in the multivariable analyses. A summary of the univariate analyses is presented in Appendix Q.

Proximity-to-death utility analyses have been used in a number of HTA submissions in oncology (160-162). A continuous predictor (log-transformed) of time-to-death was not chosen, as this approach required the assumption that censored patients are assumed dead at the time of censoring. Instead, a 28-day window was selected for the proximity to death covariate to allow sufficient utility data to be included, to align with the 28-day treatment cycle of fruquintinib, regorafenib and trifluridine-tipiracil, and for straightforward implementation with the 1-week model cycle length.

Clinical and HE experts at the UK market access advisory board (1st December 2023) advised that a multivariable model centred on baseline utility and progression status was preferable to any multivariate models that include ongoing Grade ≥3 TEAE or time-to-death, as it is the most generalisable to treatments outside of FRESCO-2. It was also highlighted that given a covariate for Grade ≥3 TEAE was omitted (47), the impact of AEs on utility can be explored separately for all treatments consistently. Therefore, this model centred on baseline utility and progression status was used in the base case (Table 48). Progression was experienced by 166 patients (represented by 213 observations) and 96 patients (represented by 113 observations) in the fruquintinib and placebo arms, respectively. In the base case multivariable model, the utility decrement for progressed disease (–0.0580, p<0.0001) was statistically significant.

Table 48: Coefficients for EQ-5D-3L UK model with centred baseline utility and progression status

Variable	Estimate	SE	Lower 95% CI	Upper 95% CI	p-value
Intercept	0.7111	0.0073	0.6968	0.7254	<0.0001
Baseline utility	0.6398	0.0399	0.5615	0.7180	<0.0001
Progressed disease	–0.0580	0.0101	–0.0777	–0.0382	<0.0001

Abbreviations: CI, confidence interval; SE, standard error; UK, United Kingdom.

Table 49 presents the base case predicted utility scores for patients who are progression-free and progressed. No difference in utility by treatment arm is modelled. Disutilities for Grade 3–4 treatment-related TEAEs are included in the economic model separately, as described in Section B.3.5.4.

Table 49: Predicted EQ-5D-3L UK utility scores

Label	Estimate	Standard Error	Lower 95% CI	Upper 95% CI
Progression-free	0.71	0.01	0.70	0.73
Post-progression	0.65	0.01	0.63	0.67

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol five-dimension three-level; PD, progressed disease; UK, United Kingdom.

Utility values are adjusted for age-and-gender matched general population utility values, as presented by Hernandez Alava (147), in line with NICE guidance. A summary of utility values used in the base case is presented in Table 51.

The utility values estimated for the progression-free health state are consistent with those used in previous NICE and SMC submissions identified by the health-related quality of life SLR (Table 50) (53). The utility decrement estimated for progressed disease vs progression-free (0.06) is comparable to TA405 (0.09), but lower than TA866 (0.13), SMC 2312 (0.11), and SMC 1221/16 (0.14).

Table 50: FRESCO-2 utility values compared with previous HTAs

Label	FRESCO-2	TA866	TA405	SMC 2312	SMC 1221/17
Progression-free	0.71	0.72	0.73	0.74	0.73
Post-progression	0.65	0.59	0.64	0.63	0.59
Progression decrement	0.06	0.13	0.09	0.11	0.14

Abbreviations: CI, confidence interval; PD, progressed disease; SMC, Scottish Medicines Consortium; TA, technology appraisal; UK, United Kingdom.

In TA866, the mean utility score at end of treatment in CORRECT and CONCUR was used to inform the progressed health state, with no formal adjustment for progression or baseline utility using a mixed regression model. This method of estimating utility values is less robust than a linear mixed model as it does not attempt to estimate health state utility values independent of baseline values. At the UK market access advisory board (1st December 2023) (47), clinical and HE experts confirmed the progression-free utility values estimated from FRESCO-2 were consistent with those in previous appraisals, however recommended that scenarios using alternative progressed disease decrements should be explored. Therefore, scenarios were conducted to explore the impact of using the decrements for post-progression vs progression-free presented in TA866 and TA405 to inform utility values for progressed disease.

Table 51: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% C interval	Reference in submission (section and page number)	Justification
Progression-free				
Fruquintinib, regorafenib, trifluridine-tipiracil, and BSC	0.71 (0.01)	0.70, 0.73	Section B.3.5.5	Utility values estimated directly from a large, worldwide RCT in a population consistent with the expected positioning of fruquintinib in UK clinical practice.
Fruquintinib AE QALY decrement (Grade ≥3 and Grade 1–2 treatment-related TEAE)	–0.0009	N/A	Section B.3.5.4	Calculated average QALY loss associated with treatment-related TEAEs by treatment
Regorafenib AE QALY decrement (Grade ≥3 and Grade 1–2 treatment-related TEAE)	–0.0015	N/A		
Trifluridine-tipiracil AE QALY decrement (Grade ≥3 and Grade 1–2 treatment-related TEAE)	–0.0030	N/A		
BSC AE QALY decrement	–0.0003	N/A		
Progressed				
Fruquintinib, regorafenib, trifluridine-tipiracil, and BSC	0.65 (0.01)	0.63, 0.67	Section B.3.5.5	Utility values estimated directly from a large, worldwide RCT in a population consistent with the expected positioning of fruquintinib in UK clinical practice.

Abbreviations: AE, adverse event; BSC, best supportive care, N/A, not applicable; RCT, randomised controlled trial.

B.3.6 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted on 23rd October 2023 to identify cost and health care resource use data in mCRC in patients 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, if *RAS* wild type, an anti-EGFR therapy. A detailed description of the SLR methods and results are reported in Appendix I.

B.3.6.1 Intervention and comparators' costs and resource use

B.3.6.2 Acquisition costs

All primary therapies in the model were costed as per the doses outlined in Section B.3.2.8. All acquisition costs were sourced from the British National Formulary (BNF). The dosing schedules associated with all therapies are consistent with the SmPC recommended dosing, as detailed in Section B.3.2.8.2 (7, 55). In accordance with the anticipated pharmacy administration schedule for fruquintinib, the model assumed patients who are still on treatment at the beginning of each 4-week treatment cycle would be dispensed all the medicine required to last them for the next 4 weeks, therefore the full per-cycle acquisition costs of fruquintinib, regorafenib and trifluridine-tipiracil are applied at the beginning of each 4-week treatment cycle in the model. This is aligned with the approach taken in TA866. The costs per pack of fruquintinib, regorafenib and trifluridine-tipiracil are presented in Table 52. In the base case, a proposed [redacted] patient access scheme [PAS] of [redacted]% is applied to the list price of fruquintinib.

Table 52: Acquisition costs

Drug	Dose	mg/tablet	Pack price	Pack size (number of tablets)
Fruquintinib (list price)	5 mg, once daily for 3 weeks, followed by 1 week off	5	£[redacted]†	21
Fruquintinib (PAS price)			£[redacted]‡	
Fruquintinib (list price)		1	£[redacted]†	
Fruquintinib (PAS price)			£[redacted]‡	
Regorafenib	160 mg, once daily for 3 weeks, followed by 1 week off	40	£3,744.00	84
Trifluridine-tipiracil	35 mg/m^2 twice daily for 5 days, followed by 2 days off. Active treatment is given for 2 weeks, followed by 2 weeks off	15	£500.00	20
		20	£666.67	20

†Proposed list price of fruquintinib to be approved.
‡ Proposed PAS price of fruquintinib to be approved.
Abbreviations: PAS, patient access scheme.

Trifluridine-tipiracil dosage is calculated using BSA; patients receive trifluridine-tipiracil twice daily at 35 mg/m^2 for 5 days, with 2 days of rest per week, for two weeks. Therefore, the proportion of patients receiving each dose band is calculated using the methods of moments

approach (163), which estimates patient weight distribution by fitting a normal distribution around the mean BSA from pooled FRESCO and FRESCO-2 data (1.78 mg/m^2, SD: 0.21). This results in a per-cycle cost of trifluridine-tipiracil of £1,815.04 after adjusting for relative dose intensity (RDI). The distribution of trifluridine-tipiracil dosing across BSA thresholds is presented in Table 53.

Table 53: Trifluridine-tipiracil cost per 28-day treatment cycle

BSA category	Dose	15 mg	20 mg	Proportion of patients	Cost per treatment cycle
<1.07	35	1	1	0.04%	£1,166.67
1.07–1.22	40	0	2	0.35%	£1,333.34
1.23–1.37	45	3	0	2.16%	£1,500.00
1.38–1.52	50	2	1	8.24%	£1,666.67
1.53–1.68	55	1	2	20.91%	£1,833.34
1.69–1.83	60	0	3	27.71%	£2,000.01
1.84–1.98	65	3	1	23.55%	£2,166.67
1.99–2.14	70	2	2	12.72%	£2,333.34
2.15–2.29	75	1	3	3.57%	£2,500.01
≥2.30	80	0	4	0.66%	£2,666.68

Abbreviations: BSA, body surface area.

As discussed in Section B.3.2.8.2, BSC consists of a variety of concomitant treatments including any treatments necessary for health and not anticipated to interfere with the study drug, excluding anti-cancer therapies. Clinical experts at the UK market access advisory board (1st December 2023) confirmed that BSC in this patient population is the same as palliative care. Therefore, the cost of BSC is assumed to be captured within the concomitant medications taken in FRESCO and FRESCO-2 (Section B.3.6.4), the cost of resource use (Section B.3.6.6), and end of life costs (Section B.3.6.8).

B.3.6.2.1 Relative dose intensity

In FRESCO, FRESCO-2 and all comparator trials, not all patients received the full dose of fruquintinib, regorafenib or trifluridine-tipiracil (9, 10, 63, 83, 102, 109, 110). Hence, RDI was applied in the model for all treatments. Fruquintinib RDI was sourced from the pooled FRESCO and FRESCO-2 data for consistency with the source of efficacy data. This also aligns with the approach taken in TA866, where regorafenib RDI was calculated using a weighted average of CORRECT and CONCUR RDI data (164). In TA866, the committee agreed that RDI is likely to be similar between treatments in practice; this is consistent with RWE that suggests a similar dose reduction for regorafenib and trifluridine-tipiracil (54% and 48%, respectively) (164). The base case therefore assumes the same RDI across all treatments, equal to the pooled fruquintinib data from FRESCO and FRESCO-2, to account

for differences in RDI definitions across comparator trials. In the base case, RDI was applied directly to the received cost per cycle for fruquintinib, regorafenib and trifluridine-tipiracil (Table 54).

Table 54: Relative dose intensity

Treatment	RDI – base case
Fruquintinib	89.6%
Regorafenib	
Trifluridine-tipiracil	

Abbreviations: RDI, relative dose intensity.

B.3.6.3 Administration costs

As all active therapies considered in this appraisal are administered orally, no administration costs were included in the model. This approach aligns with both TA405 and TA866 (7, 55).

B.3.6.4 Concomitant medication

The cost of concomitant medications was used to represent the cost of BSC. A summary of concomitant medication received by ≥10% of patients in either arm of pooled FRESCO and FRESCO-2 data is presented in Table 55. The cost of concomitant medication in the regorafenib and trifluridine-tipiracil arms is assumed to be equivalent to the fruquintinib arm, based on clinical feedback that BSC is not expected to differ between treatment arms (47). These proportions were combined with costs per week of specific regimens (Table 56) to estimate total concomitant medication costs for all relevant comparators.

Table 55: Concomitant medication

Concomitant medication	Fruquintinib (N=739), n (%)	BSC (N=368), n (%)
Analgesics	573 (77.5)	218 (59.2)
Anti-inflammatory and anti-rheumatic products	221 (29.9)	100 (27.2)
Psycholeptics	197 (26.7)	70 (19)
Drugs for constipation	163 (22.1)	100 (27.2)
Corticosteroids for systemic use	178 (24.1)	82 (22.3)
Anti-emetics and anti-nauseants	150 (20.3)	68 (18.5)
Diuretics	144 (19.5)	65 (17.7)
Blood substitutes and perfusion solutions	143 (19.4)	53 (14.4)
Drugs for functional gastrointestinal disorders	120 (16.2)	49 (13.3)
Mineral supplements	116 (15.7)	48 (13)
Vitamins	101 (13.7)	40 (10.9)

Abbreviations: BSC, best supportive care.

A representative therapy for each concomitant medication was chosen based on the most common treatments received in FRESCO and FRESCO-2. All costs and recommended

doses were taken from the BNF (Table 56). No administration costs were assigned to concomitant medications.

Table 56: Concomitant medication specific regimens and costs per week, pooled data

Concomitant medication	Representative therapy	Strength per unit (mg)	Units per pack	Cost per pack	Dose per week (mg)	Cost per week
Analgesics	Paracetamol	500	100	£2.34	28000	£1.31
Anti-inflammatory and anti-rheumatic products	Ibuprofen	400	84	£2.87	11200	£0.96
Psycholeptics	Lorazepam	1	28	£1.41	14	£0.71
Drugs for constipation	Macrogol 3350	1	20	£3.29	21	£3.45
Corticosteroids for systemic use	dexamethasone	2	50	£3.13	280	£8.76
Anti-emetics and anti-nauseants	Metoclopramide	10	28	£0.35	210	£0.26
Diuretics	Furosemide	40	100	£0.57	280	£0.04
Blood substitutes and perfusion solutions	Sodium chloride	1	100	£9.20	28	£2.58
Drugs for functional gastrointestinal disorders	Metoclopramide	10	28	£0.35	210	£0.26
Mineral supplements	Potassium chloride	600	30	£20.19	21000	£23.56
Vitamins	Colecalciferol	400	60	£1.70	2800	£0.20

Abbreviations: BSC, best supportive care.

B.3.6.5 Subsequent treatment costs

Subsequent therapy costs were included in the analysis to align with the clinical pathway of care in mCRC (Section B.1.3.4) and the committee preferred assumptions in TA866 (7). For fruquintinib, the proportion of patients receiving subsequent therapies was informed by pooled data from FRESCO and FRESCO-2. Due to the absence of subsequent therapy data reported in each of the comparator trials for regorafenib and trifluridine-tipiracil, subsequent therapy proportions were assumed equal to fruquintinib, removing the repeat use of the primary therapy, and reweighting the proportions to sum to 1. Given the poor survival outcomes for patients with mCRC, subsequent therapy costs were assigned assuming a one-week treatment duration, as per the committee's preferred assumptions in TA866 and TA405. A scenario is presented in which the duration of treatment for subsequent therapies is two weeks. The cost of subsequent therapy was assumed to be a one-off cost at the point of progression in the model, in line with TA866. All weight-based treatments were assumed to incur drug wastage.

The pooled dataset was created using subsequent therapies received by ≥2% of patients in either arm of FRESCO (Table 58) and FRESCO-2 (Table 57). A 2% cut-off was chosen to ensure the majority of therapies were captured in the analysis and align with the methods used for AE data (Section B.3.4). Subsequent therapy data from FRESCO were reported by therapy class as opposed to by specific regimens, therefore, a representative therapy was assigned to each therapy class based on the most common therapies of each class received by patients in FRESCO-2. Surgery, 'others', and investigational drug were excluded from the analysis. The FRESCO data were combined with FRESCO-2 and re-weighted to sum to 1 to create a pooled FRESCO and FRESCO-2 dataset for use in the model (Table 59).

Table 57: Subsequent therapies received by ≥2% of patients, FRESCO-2

Subsequent therapy	Fruquintinib (N=456), n (%)	BSC (N=230), n (%)
At least one subsequent therapy	134 (29.4)	79 (34.3)
Fluorouracil	35 (7.7)	22 (9.6)
Regorafenib	34 (7.5)	18 (7.8)
Oxaliplatin	29 (6.4)	15 (6.5)
Bevacizumab	21 (4.6)	15 (6.5)
Folinic acid	18 (3.9)	12 (5.2)
Capecitabine	25 (5.5)	10 (4.3)
Irinotecan	22 (4.8)	10 (4.3)
Calcium folinate	7 (1.5)	5 (2.2)
Folinic acid, fluorouracil, oxaliplatin	3 (0.7)	5 (2.2)
Trifluridine-tipiracil	10 (2.2)	4 (1.7)
Cetuximab	9 (2.0)	4 (1.7)

Abbreviations: BSC, best supportive care.

Table 58: Subsequent therapies received by ≥2% of patients, FRESCO

Subsequent therapy	Assigned therapy	Fruquintinib (N = 278) n (%)	BSC (N = 138) n (%)
At least one subsequent therapy	N/A	118 (42.4)	70 (50.7)
Chemotherapy	Fluorouracil	90 (32.4)	61 (44.2)
Radiotherapy	N/A	19 (6.8)	6 (4.3)
Surgery	N/A	13 (4.7)	6 (4.3)
Others	N/A	14 (15.8)	23 (16.7)
Anti-VEGF/VEGFR, does not contain anti-EGFR	Bevacizumab	30 (10.8)	22 (15.9)
Anti-EGFR, does not contain anti-VEGF/VEGFR	Cetuximab	8 (2.9)	6 (4.3)
Investigational drug	N/A	7 (2.5)	14 (10.1)

Abbreviations: BSC, best supportive care; EGFR, epidermal growth factor receptor; N/A, not applicable; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

At the UK market access advisory board (1st December 2023) (47), clinicians advised that patients receiving BSC would be unlikely to receive any further anti-cancer therapy. Therefore, in the base case, it is assumed that no patients receive subsequent therapies in the BSC arm. A scenario analysis was conducted which uses the proportions based on the pooled FRESCO and FRESCO-2 data for the BSC arm (Table 59).

Table 59: Subsequent therapies used in the model, pooled FRESCO and FRESCO-2 data

Subsequent therapy	Fruquintinib (%)	Regorafenib (%)	Trifluridine-tipiracil (%)	BSC (%) – scenario only
At least 1 subsequent therapy	34.3	34.3	34.3	40.5
Fluorouracil	34.7	38.3	35.7	38.6
Regorafenib	9.4	0.0	9.7	8.4
Oxaliplatin	8.1	8.9	8.3	7.0
Bevacizumab	14.2	15.6	14.6	17.2
Folinic acid	5.0	5.5	5.1	5.6
Capecitabine	6.9	7.7	7.1	4.7
Irinotecan	6.1	6.7	6.3	4.7
Calcium folinate	1.9	2.1	2.0	2.3
Folinic acid, fluorouracil, oxaliplatin	0.8	0.9	0.9	2.3
Trifluridine-tipiracil	2.8	3.1	0.0	1.9
Cetuximab	4.7	5.2	4.9	4.7
Radiotherapy	5.3	5.8	5.4	2.8
Source	Pooled FRESCO and FRESCO-2 data	Pooled FRESCO and FRESCO-2 data, removing regorafenib use	Pooled FRESCO + FRESCO-2 data, removing trifluridine-tipiracil use	Pooled FRESCO and FRESCO-2 data

Abbreviations: BSC, best supportive care.

Subsequent treatment proportions were informed by the pooled FRESCO and FRESCO-2 data in the base case for alignment with cost and efficacy input data. However, some of the subsequent therapies received in FRESCO and FRESCO-2, for example anti-VEGF/VEGFR therapies (bevacizumab), are not recommended by NICE for use in mCRC. Therefore, a scenario was conducted which explored subsequent therapy distributions based on clinical opinion elicited at the UK market access advisory board (1st December 2023) (47).

Clinicians advised that a small proportion of patients would be well enough to receive subsequent anti-cancer therapy, and that these patients would receive either regorafenib or trifluridine-tipiracil, depending on the treatment they received as a primary therapy, with the remainder of patients receiving palliative care. Clinicians stated that fewer patients would be well enough to tolerate further treatment after regorafenib compared with fruquintinib and trifluridine-tipiracil due to the toxicity profile of regorafenib. Clinicians also stated that some patients would be accepted onto clinical trials. However, to align with NICE reference case, the proportion of patients going on to clinical trials were removed, and the remaining proportions reweighted to sum to 100%. These values are presented in Table 60. The

impact of this scenario is small; subsequent therapy costs are not a significant driver of cost-effectiveness (Section B.3.12.3).

Table 60: Subsequent therapies, scenario analysis

Primary treatment	Proportion receiving subsequent anti-cancer treatment	Subsequent therapy: regorafenib (%)	Subsequent therapy: trifluridine-tipiracil (%)
Fruquintinib	20%	0%	100%
Regorafenib	5%	0%	100%
Trifluridine-tipiracil	20%	100%	0%
BSC	0%	0%	0%

Abbreviations: BSC, best supportive care.

Administration costs for subsequent therapies are described in Table 61. Individual therapies are assigned the cost of a simple infusion and combination therapies are assigned the cost of a complex infusion. A summary of the unit costs of subsequent therapies is presented in Table 62. Radiotherapy is assigned a cost of £1,037 based on a weighted average of NHS reference costs for outpatient radiotherapy (cost codes: SC21Z:SC56Z, £207), assuming a course of five doses, based on a one-week subsequent therapy duration and short-course radiotherapy schedule used in CRC (165).

Table 61: Subsequent therapy administration costs

Route of administration	Administration cost (per dose)	Source
IV infusion, first attendance	£287	NHS reference costs, Deliver Simple Parenteral Chemotherapy at First Attendance, SB12Z (166).
IV infusion, first attendance, more complex chemotherapy	£354	NHS reference costs, Deliver more Complex Parenteral Chemotherapy at First Attendance: SB13Z (166).
IV infusion, subsequent delivery	£475	NHS reference costs, Deliver Subsequent Elements of a Chemotherapy Cycle. SB15Z (166)
Oral	£0	Assumption

Abbreviations: IV, intravenous.; NHS, national schedule of reference costs.

Table 62: Subsequent therapy costs

Concomitant medication	Strength per unit (mg/ml)	Units per Pack	Cost per pack	Dose per admin	No of admin (1-week cycle)	Drug cost (1-week cycle)	Admin cost (1-week cycle)
Fluorouracil	500	1	£3	400	7	£48	£3,136
Oxaliplatin	50	1	£20	85	7	£505	£3,136
Capecitabine	150	60	£9	1,250	14	£32	£0
Irinotecan	100	1	£13	350	7	£604	£3,136
Regorafenib	40	84	£3,744	160	7	£1,248	£0
Bevacizumab	25	4	£205	5	1	£822	£287
Cetuximab	5	20	£178	500	7	£837	£49
Trifluridine-tipiracil	15	20	£500	35	10	£1,038	£0
Folinic acid	300	1	£33	350	1	£268	£3,136
Calcium folinate	15	10	£9	350	7	£143	£0

B.3.6.6 Health-state unit costs and resource use

No additional medical resource use (MRU) data were identified by the cost and resource use SLR (Appendix I) to those presented in NICE TA866. Therefore, MRU frequencies were sourced from NICE TA866 and validated at the UK market access advisory board (1st December 2023); clinicians broadly agreed on the elements of resource use applied in the model. Clinicians also agreed that resource use for all active therapies is the same in UK clinical practice, and that resource use post-progression is the same regardless of treatment. A scenario is presented that uses a mean of the resource use frequencies estimated by clinicians at the UK market access advisory board (1st December 2023). The impact of this scenario is small given that resource use is not a significant driver of cost-effectiveness (Section B.3.12.3). Costs were sourced from the NHS reference costs for 2021/22 and the 2022 Personal Social Services Research Unit (PSSRU) costs. Resource use estimates are summarised in Table 63.

Table 63: Medical resource use and costs

Element of resource use	Resource use frequency (per month), TA866, base case			Resource use frequency (per month), clinical input, scenario			Unit costs	Source
	Progression-free		Post-progression	Progression-free	Post-progression	Post-progression		
	Active treatment	BSC		Active treatment	BSC			
GP surgery visit	0	0	1	0.33	0.50	0.50	£42.00	PSSRU, 2022 (167) Unit costs for a GP per surgery consultation lasting 9.22 minutes (including indirect costs)
GP home consultation	0	0	0.25	0	0	0	£271.00	PSSRU, 2022 (167) Unit costs for a GP per hour of patient contact (including indirect costs)
Community nurse specialist visit	0	0	1	0.33	0.33	0.67	£57.00	PSSRU, 2022 (167) band 6 nurse, cost per working hour
Home care worker/health home visitor	0.25	0.25	1	0.33	0.50	0.67	£23.00	PSSRU, 2022 (167) home care worker per weekday hour
District nurse visit	0	0	1	0.33	0.33	0.33	£54.00	NHS ref costs 2021/22 code: N02AF (166)
CT scan	0.33	0	0	0.61	0.11	0	£182.00	NHS ref costs 2021/22 code: RD22Z (166)
Medical oncologist outpatient visit	0	0	0	0.83	0.33	0	£293.00	NHS ref costs 2021/22 code: 370 (166)
Oral chemotherapy outpatient	1	0	0	0	0	0	£197.00	NHS ref costs 2021/22 code: SB11Z (166)
Liver function test	0	0	0	1	0.33	0	£1.55	NHS ref costs 2021/22 code: DAPS04 (166)
Renal function test	0	0	0	1	0.33	0	£1.55	NHS ref costs 2021/22 code: DAPS04 (166)
Full blood count	0	0	0	1	0.33	0	£2.39	NHS ref costs 2021/22 code: DAPS03 (166)

Abbreviations: BSC, best supportive care; CT, computerised tomography; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.6.7 Adverse reaction unit costs and resource use

A list of the treatment-related TEAEs included in the model, and the corresponding frequencies are presented in Section B.3.4. AE costs were mostly obtained from the NHS reference costs 2021/2022, or sourced from prior NICE TAs when NHS reference costs were unavailable. Where relevant, costs were inflated to the 2022 cost year using the PSSRU inflation indices (167). Unit costs for Grade 3 or above AEs are presented in Table 64. As discussed in Section B.3.4, clinicians advised that the majority of AEs resolve soon after onset, and are experienced early on in a patient's treatment, therefore AE proportions are combined with unit costs in the model and applied as a one-off cost in the first model cycle. Grade 1and 2 AEs included in the model are assigned a flat cost of £5 per event in the model as per the committee preferred assumption in TA866, in the absence of other data (7).

Table 64: Adverse event unit costs

Adverse event	Unit cost (CI)	Source
Anaemia	£1,439.66 (£1,151.73, £1,727.59)	NHS ref costs 2021/22 weighted average of codes SA04G,H,J,K,L (NES and NEL)
Asthenia	£14.41 (£11.53, £17.29)	NHS ref costs 2021/22 code: WH17
Diarrhoea	£691.97 (£553.57, £830.36)	NHS ref costs 2021/22 weighted average of codes PF26A&B (NES)
Fatigue	£14.41 (£11.53, £17.29)	NICE ERG report abiraterone (TA259), table 24, p. 64, inflated to 2022
Hand foot syndrome/Palmar-plantar erythrodysesthesia	£174.10 (£139.28, £208.93)	NHS ref costs 2021/22 code: 300 (Outpatient consultant-led)
Hypertension	£770.10 (£616.08, £924.12)	NHS ref costs 2021/22 code: EB04Z
Increased aspartate aminotransferase	£174.10 (£139.28, £208.93)	NHS ref costs 2021/22 code: 300 (Outpatient consultant-led)
Increased total bilirubin	£174.10 (£139.28, £208.93)	NHS ref costs 2021/22 code: 300 (Outpatient consultant-led)
Leukopenia	£191.36 (£153.09, £229.63)	Assumed equal to neutropenia cost as per EAG in TA405
Neutropenia	£191.36 (£153.09, £229.63)	TA405 EAG preferred cost inflated to 2022 using the PSSRU inflation indices
Rash	£174.10 (£139.28, £208.93)	NHS ref costs 2021/22 code: 300 (Outpatient consultant-led)
Thrombocytopenia	£2,163.38 (£1,730.7, £2,596.06)	NHS ref costs 2021/22 weighted average of codes SA12G,H,J,K (NES and NEL)
Lymphopenia	£191.36 (£153.09, £229.63)	Assumed equal to leukopenia as per TA866

Adverse event	Unit cost (CI)	Source
Proteineuria	£174.10 (£139.28, £208.93)	NHS ref costs 2021/22 code: 300 (Outpatient consultant-led)
Anorexia	£174.10 (£139.28, £208.93)	NHS ref costs 2021/22 code: 300 (Outpatient consultant-led)
Decreased appetite	£174.10 (£139.28, £208.93)	Assumed equal to leukopenia as per TA866
Febrile neutropenia	£3,022.73 (£2,418.18, £3,627.28)	The NICE DSU report on the cost of febrile neutropenia 2007, inflated to 2021
Mucositis	£174.10 (£139.28, £208.93)	Assumed equal to leukopenia as per TA866
Hypophosphataemia	£174.10 (£139.28, £208.93)	Assumed equal to leukopenia as per TA866
Lipase level increased	£174.10 (£139.28, £208.93)	Assumed equal to leukopenia as per TA866

Abbreviations: BSC, best supportive care; CT, computerised tomography; ERG, evidence review group; GP, general practitioner; NEL, non-elective long stay; NES, non-elective short stay; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

A summary of the total AE costs applied to each treatment arm is presented in Table 65.

Table 65: One-off cost of AEs, by treatment arm

Primary treatment	Fruquintinib	Regorafenib	Trifluridine-tipiracil	BSC
Total cost of AEs	£180.10	£290.94	£630.60	£41.62

Abbreviations: AE, adverse event; BSC, best supportive care.

B.3.6.8 Miscellaneous unit costs and resource use

A one-off end-of-life care cost was assigned to each patient upon death. As no more recent data were identified to inform the cost of end-of-life care in the cost and resource use SLR (Section B.3.6.6), this was sourced from healthcare and social care costs estimated in Round et al (168) for mCRC as per TA866. After adjusting for inflation using the PSSRU inflation indices, the total cost per death was estimated to be £7,192 (CI: £5,753–£8,630), applied to all incident deaths in the model.

B.3.7 Severity

As described in Section B.1.3.3, patients with mCRC have significantly worse survival outcomes and HRQoL vs the general population. This is reinforced by the estimated absolute and proportional QALY shortfall estimates for each comparator (Table 68).

To assess the severity of mCRC, absolute and proportional QALY shortfalls were calculated as per the NICE methods guide. The QALYs for the general population without the condition over their remaining lifetime were estimated using national life tables for England from 2018-2020 (137) and utilities based on the Hernandez-Alava algorithm (169). A mean starting age

of 59.4 years and a 57.8% male population is assumed as per the pooled FRESCO and FRESCO-2 trial data (Table 66), which was considered by clinicians to be representative of those who receive standard of care treatments, and expected to receive fruquintinib, in UK clinical practice (47). Patients without the disease have expected undiscounted life years of 24.6 and 12.9 remaining discounted QALYs.

Expected QALYs and life years for patients with the disease were informed by the economic model using the base case settings. Patients with the disease who receive BSC, regorafenib and trifluridine-tipiracil are expected to accrue 0.63, 0.87 and 0.89 undiscounted life years, respectively and have an expected 0.42, 0.57 and 0.58 remaining discounted QALYs, leading to an absolute QALY shortfall of 12.48, 12.32 and 12.31, respectively, and a proportional QALY shortfall of 0.97, 0.96 and 0.96, respectively. The resulting absolute and proportional shortfall values lie in the range of 12.31 to 12.48, and 0.96 to 0.97 across modelled comparator treatments, respectively. This suggests that a 1.7 x QALY severity multiplier is appropriate and as a result, a WTP threshold of £51,000 per QALY is relevant in this analysis vs all comparators. This is in line with TA866, which indicated a WTP threshold of £51,000 per QALY for all analyses conducted by the company and EAG for comparisons with both trifluridine-tipiracil and BSC, and TA405, for which the end-of-life criteria previously considered by NICE were judged to be met (44, 53).

Table 66: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
% male	57.8% (Table 30)	Section B.3.3.1
Starting age	59.4 (Table 30)	

Table 67: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years†
Progression-free	0.71 (0.01)	0.29 (regorafenib) 0.29 (trifluridine-tipiracil) 0.19 (BSC)
Progressed	0.65 (0.01)	0.59 (regorafenib) 0.60 (trifluridine-tipiracil) 0.44 (BSC)

†sum of undiscounted life years in this table do not exactly match the total in the text due to rounding.

Table 68: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute (proportional) QALY shortfall
12.89	Regorafenib:0.57	12.32 (0.96)
	Trifluridine-tipiracil:0.58	12.31 (0.96)
	BSC: 0.42	12.48 (0.97)

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

In all scenarios conducted which influence QALY estimates, presented in Section B.3.12.3., the severity modifier remains 1.7 vs BSC, regorafenib and trifluridine-tipiracil, demonstrating the robustness of the severity modifier estimates to changing assumptions.

In TA866, the committee raised concerns over the appropriateness of the data used to inform QALY shortfall estimates, as the trials underpinning these estimates had their primary completion between 2011 and 2013, which was deemed outdated considering the advancement in the management of mCRC since these trials were conducted. The data informing the base case estimates in this appraisal are more recent than those presented in TA866. Specifically, the primary completion dates of FRESCO and FRESCO-2 were 2017 and 2022, respectively. Moreover, as shown in Section B.3.15.3, estimated median OS and PFS are consistent with those reported in real world data (RWD). Of the RWD identified by the clinical SLR (Appendix D (section D.2.4) two were UK-based studies, both presenting data on the use of trifluridine-tipiracil in UK clinical practice. The median OS (7.6-5.8 months) and PFS (3.3-3.2 months) in each of these studies is aligned with modelled estimates ([redacted] months and [redacted] months for OS and PFS, respectively in both arms). At the UK market access advisory board (1st December 2023) (47), clinical experts agreed that the characterisation of BSC was consistent between FRESCO and FRESCO-2, and was representative of UK clinical practice. Using data from FRESCO and FRESCO-2 to inform QALY shortfall estimates was therefore considered appropriate.

B.3.8 Uncertainty

The key uncertainties in most oncology economic evaluations are typically estimates of long-term survival for model comparators, for example the extrapolation of trial survival data and methods used to estimate comparative efficacy estimates for which patient level data is unavailable.

As discussed in B.3.3.2.1, B.3.3.2.2, and B.3.3.2.3, clinical data from FRESCO and FRESCO-2, the two large, Phase III randomised, placebo-controlled trials assessing fruquintinib in the relevant population that were used to inform key clinical inputs in the

model, were mature. In the pooled dataset, 68% and 77% of patients had experienced an OS event, 85% and 92% of patients had experienced a progression event, and 94% and 99% of patients had discontinued treatment in the fruquintinib and BSC arms, respectively. The maturity of these trial data meant there was little variation in the long-term survival extrapolations estimated using the seven standard parametric distributions for each endpoint. Furthermore, modelled median OS and PFS estimates, as well as landmark survival estimates, were well aligned with the observed KM data, clinical opinion on expected survival in UK practice, and published data in the literature.

As no direct head-to-head evidence was available to inform the comparison of fruquintinib with regorafenib and trifluridine-tipiracil, comparative efficacy estimates were informed by the NMA. Although predicted survival in the regorafenib and trifluridine-tipiracil arms of the model were consistent with estimates reported in key clinical trials and RWE (Section B.3.3.2.1), extensive scenario analyses were conducted to assess the uncertainty in these comparative efficacy estimates. All trials included in the NMA were considered comparable (Section B.2.9.2), with some minor imbalances in patient baseline characteristics identified between trials. Clinical opinion advised that these imbalances are unlikely to impact outcomes and that it was not necessary to adjust for any potential treatment effect modifiers in this population. However, a series of scenario analyses were conducted to explore the potential impact of these imbalances on NMA results (as discussed in Section B.2.9.6) (123). As discussed in Section B.2.9, results are consistent across NMA scenarios, and support the conclusion that there is minimal impact associated with heterogeneity in patient populations across comparator trials. At the UK market access advisory board (1st December 2023) (47), clinical and HE experts were in agreement that the consistency of results across NMA scenarios reduced uncertainty associated with the conclusions.

To further demonstrate the robustness of the model results, uncertainty was explored through extensive univariate sensitivity analysis, probabilistic sensitivity analysis (PSA) and scenario analyses.

In the PSA, all parameters were assigned distributions and varied jointly. 10,000 MC simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on a cost-effectiveness plane (CEP), and a cost-effectiveness acceptability curve (CEAC) was generated. Uncertainty related to the condition and data informing the model is discussed in Section B.3.16. Sensitivity analyses exploring structural uncertainties is also described in Sections B.3.12 and alternative assumptions are explored in scenario analysis, described in Section B.3.12.3.

B.3.9 Managed access proposal

The company's preferred funding of fruquintinib for [redacted] is through routine NHS funding via baseline commissioning. This is consistent with the maturity of both the FRESCO and FRESCO-2 datasets that inform the model. However, should the NICE committee feel unable to make a positive recommendation for routine NHS funding, Takeda would be open to discussions with NICE and NHS England to explore potential inclusion in the Cancer Drugs Fund.

B.3.10 Summary of base case analysis inputs and assumptions

B.3.10.1 Summary of base case analysis inputs

A summary of the base case inputs is provided in Table 69.

Table 69: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
General parameters			
Discount rate, costs	3.5%	Fixed	Section B.3.2.5
Discount rate, outcomes	3.5%	Fixed	Section B.3.2.5
Time horizon	Lifetime (10 years)	Fixed	Section B.3.2.3
Baseline age, years	59.4	Normal (CI: 37.9–80.9)	Section B.3.3.2
Male, %	57.8%	Beta (CI: 54.9–60.7)	Section B.3.3.2
Body weight, kg	70.17	Normal (CI: 38.7–101.7)	Section B.3.3.2
BSA, m^2	1.78	Normal (CI: 1.4–2.2)	Section B.3.3.2
Survival curves			
OS curve choice;	Joint models; Fruq and BSC: Generalised gamma (Treatment predictor: [redacted]; mu: [redacted]; sigma: [redacted]; Q: [redacted])	Multivariate normal	Section B.3.3.2.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
PFS curve choice	Joint models; Fruq and BSC: Log-normal (treatment predictor: [redacted]; Meanlog: [redacted]; SDlog: [redacted])	Multivariate normal	Section B.3.3.2.2
TTD curve choice	Fruq independent: Log-normal (Meanlog: [redacted]; SDlog: [redacted])	Multivariate normal	Section B.3.3.2.3
OS HR vs fruquintinib	T/T: [redacted] Reg: [redacted]	T/T: Log-normal (CrI, [redacted]) Reg: Log-normal (CrI, [redacted])	Section B.3.3.2.1
PFS/TTD HR vs fruquintinib	T/T: [redacted] Reg: [redacted]	T/T: Log-normal (CrI, [redacted]) Reg: Log-normal (CrI, [redacted])	Section B.3.3.2.2
Adverse events			
Grade ≥3 treatment-related TEAEs	Table 42	Beta	Section B.3.4
Grade 1–2 treatment-related TEAEs	Appendix N	Beta	Appendix N
Utility values			
Utility model selection	Model with baseline utility and progression status, FRESCO-2) Intercept: 0.7111 Post-progression: –0.0580	Multivariate normal ; Intercept (CI: 0.6968–0.7254) Post-progression (CI: –0.0777, –0.0382)	Section B.3.5.5
AE disutility, anaemia	0.0900	Beta (CI: 0.07-0.11)	Section B.3.5.4
AE disutility, asthenia	0.1150	Beta (CI: 0.09-0.14)	
AE disutility, diarrhoea	0.1030	Beta (CI: 0.08-0.12)	
AE disutility, fatigue	0.1150	Beta (CI: 0.09-0.14)	
AE disutility, hand-foot syndrome/palmar-plantar erythrodysesthesia	0.0320	Beta (CI: 0.03-0.04)	
AE disutility, hypertension	0.0000	Not varied	
AE disutility, aspartate aminotransferase increased	0.0900	Beta (CI: 0.07-0.11)	
AE disutility, blood bilirubin increased	0.0900	Beta (CI: 0.07-0.11)	
AE disutility, leukopenia	0.0900	Beta (CI: 0.07-0.11)	
AE disutility, neutropenia	0.0900	Beta (CI: 0.07-0.11)	
AE disutility, rash	0.0320	Beta (CI: 0.03-0.04)	
AE disutility, thrombocytopenia	0.0900	Beta (CI: 0.07-0.11)	
AE disutility, lymphopenia	0.0900	Beta (CI: 0.07-0.11)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
AE disutility, proteinuria	0.0900	Beta (CI: 0.07-0.11)	
AE disutility, anorexia	0.1030	Beta (CI: 0.08-0.12)	
AE disutility, decreased appetite	0.1030	Beta (CI: 0.08-0.12)	
AE disutility, febrile neutropenia	0.1150	Beta (CI: 0.09-0.14)	
AE disutility, mucositis	0.0320	Beta (CI: 0.03-0.04)	
AE disutility, hypophosphataemia	0.0900	Beta (CI: 0.07-0.11)	
AE disutility, lipase level increased	0.0900	Beta (CI: 0.07-0.11)	
Grade 1–2 AE disutility	0.0100	Beta (CI: 0.01-0.01)	
Drug costs			
Fruq cost per pack (5mg, list)	[redacted]	Fixed	Section B.3.6.2
Fruq cost per pack (1mg, list)	[redacted]	Fixed	
Fruq cost per pack (5mg, PAS)	[redacted]	Fixed	
Fruq cost per pack (1mg, list)	[redacted]	Fixed	
T/T cost per pack (15 mg)	£500.00	Fixed	
T/T cost per pack (20 mg)	£666.67	Fixed	
Reg cost per pack	£3,744.00	Fixed	
Fruq, T/T, reg RDI (Pooled FRESCO and FRESCO-2)	89.6%	Beta (CI: 88.4–90.7)	Section B.3.6.2.1
Subsequent treatments			
Proportion of patients	Table 60	Beta (CI: +/- 20% around mean)	Section B.3.6.5
Fluorouracil cost per pack	£3	Fixed	
Oxaliplatin cost per pack	£20	Fixed	
Capecitabine cost per pack	£9	Fixed	
Irinotecan cost per pack	£13	Fixed	
Regorafenib cost per pack	£3,744	Fixed	
Bevacizumab cost per pack	£205	Fixed	
Cetuximab cost per pack	£178	Fixed	
Trifluridine-tipiracil cost per pack	£500	Fixed	
Radiotherapy cost	£207	Fixed	
Folinic acid cost per pack	£33	Fixed	
Calcium folinate cost per pack	£9	Fixed	
Administration costs			
IV infusion, first attendance	£287	Gamma (CI: 229.4-344.1)	Section B.3.6.5
IV infusion, first attendance, complex infusion	£354	Gamma (CI: 282.91-424.37)	
IV infusion, first attendance, prolonged infusion	£441	Gamma (CI: 352.27-528.85)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
IV infusion, subsequent delivery	£475	Gamma (CI: 380.0-569.9)	
Concomitant medication			
Concomitant medication proportions	Table 56	Beta (CI: +/- 20% around mean)	Section B.3.6.4
Concomitant medication costs	Table 55	Fixed	
AE costs			
Unit costs	Table 64	Gamma (CI: +/- 20% around mean)	Section B.3.6.7
Resource use costs			
Progression-free, frequency of oral chemotherapy day-case	0.25	Gamma (CI: 0.23-0.31)	Section B.3.6.6
Progression-free, frequency of health home visit	0.06	Gamma (CI: 0.04-0.14)	
Progression-free, frequency of CT scan	0.08	Gamma (CI: 0.06-0.11)	
Progression-free, frequency of medical oncologist outpatient visit	0.25	Gamma (CI: 0.23-0.11)	
Progressed, frequency of GP home consultation	0.06	Gamma (CI: 0.04-0.11)	
Progressed, frequency of community nurse specialist visit	0.25	Gamma (CI: 0.23-0.11)	
Progressed, frequency of health home visit	0.25	Gamma (CI: 0.23-0.11)	
Progressed, frequency of district nurse visit	0.25	Gamma (CI: 0.24-0.04)	
Progressed, frequency of GP surgery visit	0.25	Gamma (CI: 0.23-0.11)	
GP surgery visit	£42.00	Gamma (CI: 33.6-50.4)	
GP home consultation	£271.00	Gamma (CI: 216.8-325.2)	
Community nurse specialist visit	£57.00	Gamma (CI: 45.6-68.4)	
Home care worker/health home visitor	£23.00	Gamma (CI: 18.4-27.6)	
District nurse visit	£54.00	Gamma (CI: 43.2-64.8)	
CT scan	£182.00	Gamma (CI: 145.6-218.4)	
Medical oncologist outpatient visit	£293.00	Gamma (CI: 234.4-351.6)	
Oral chemotherapy outpatient	£197.00	Gamma (CI: 157.6-236.4)	
Liver function test	£2.96	Gamma (CI: 2.4 – 3.6)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Renal function test	£2.96	Gamma (CI: 2.4 – 3.6)	
Full blood count	£1.55	Gamma (CI: 1.2 – 1.9)	
End of life costs	£7,191.72	Gamma (CI: 5753.38-8630.06)	Section B.3.6.8

Abbreviations: AE, adverse event; BSA, body surface area; CI, confidence interval; Fruq, fruquintinib; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; Reg, regorafenib; TTD, time to treatment discontinuation; T/T, trifluridine-tipiracil.

B.3.10.2 Assumptions

A summary of assumptions is presented in Table 70.

Table 70: Assumptions used in the economic model

Assumption	Justification
Pooling the FRESCO and FRESCO-2 trials provides outcomes reflective of a UK population, and is the most robust source of evidence for decision-making	Data from the two available Phase III randomised, placebo-controlled trials, FRESCO and FRESCO-2, were pooled. This was considered the best use of the evidence base as this approach: • Utilises both large, blinded, Phase III RCTs which assessed fruquintinib vs BSC in the population of interest • Reflects a population that is more representative of the UK landscape vs using FRESCO or FRESCO-2 independently (described further below) • Provides a greater sample size to inform analyses, and hence reduce uncertainty in clinical inputs in the economic model • Aligns with the approach conducted in TA866 and TA405 (7, 55), and specifically the NICE committee preferences in both appraisals. As described in Section B.2.3.3 and B.2.5, advisors at the UK oncologist advisory board (22nd September 2023) highlighted that FRESCO is considered representative of the UK population's current low rate of exposure to anti-VEGF treatments (e.g. bevacizumab), while FRESCO-2 is considered representative of the UK population with respect to ethnicity (11). Considering both an Asian-only and a global study together aligns with the prior NICE appraisal in previously treated mCRC, TA866 and TA405. Prior exposure to anti-VEGF therapy may reduce the treatment effect of fruquintinib vs BSC, given the mechanism of action targets some of the same anti-angiogenic pathways (18). The same statement was made during the appraisal of regorafenib (7). Therefore, FRESCO, FRESCO-2 and the pooled dataset may underestimate the relative effect of fruquintinib vs BSC in a UK population. Uncertainty in efficacy inputs has been explored in the model through sensitivity analysis (Sections B.3.3.2and B.2.6.3).

Assumption	Justification
The proportional hazard assumption holds between fruquintinib and BSC OS and PFS	Assessment of the log-cumulative hazard plot and quantile-quantile plots suggest that there is no violation of the proportional hazards assumption and that the treatment effect may be constant over time, therefore, joint survival models were considered appropriate for both OS and PFS. At the UK market access advisory board (1st December 2023), clinicians stated they did not expect to see any differences between the hazard profiles of each comparator (47).
The relative effect for PFS for regorafenib and trifluridine-tipiracil vs fruquintinib is an appropriate proxy for TTD	Patients on trifluridine-tipiracil and regorafenib are treated until progression, which means that in clinical practice, PFS and TTD are likely to be similar. This is consistent with the observed PFS and TTD data from FRESCO and FRESCO-2 (Section B.3.3.2.3), and aligns with the assumption in TA866 (7).
Utility values are dependent on progression status	Predictors of HRQoL were tested through univariate regression analysis. Covariates that were statistically significant predictors of utility were retained for consideration in the analysis. Progression status, ongoing TEAE, and time to death remained statistically significant in the multivariate analysis. A utility model including only progression-status was used in the base case, as this was considered more generalisable to comparators not included in FRESCO-2 by HE experts. Estimated health state utility values were consistent with previous appraisals, and scenario analyses were conducted to explore uncertainty in the PF vs PD utility decrement.
The majority of treatment related AEs occur at the beginning of treatment with most resolving soon after onset	Clinical experts at the UK market access advisory board (1st December 2023) advised that the majority of AEs occur at the beginning of treatment with most resolving soon after treatment starts (47), therefore the impact of AEs is assessed as a one-off cost and QALY loss at the beginning of treatment.
RDI is assumed to be equivalent for fruquintinib, regorafenib, and trifluridine-tipiracil	RDI was assumed equal to the fruquintinib RDI estimated from the pooled FRESCO and FRESCO-2 data in the base case to align with the committee's preferred assumption in TA866.
BSC treatment cost is not expected to differ from concomitant medication	Clinical experts at the UK market access advisory board (1st December 2023) advised that BSC is broadly equivalent to palliative care (47). Therefore, it was assumed that the cost of BSC is captured by the concomitant medications received in FRESCO and FRESCO-2.
Oral therapies are not assumed to incur an administration cost	In line with TA866 and TA405 and given that all considered active therapies are administered orally, no administration costs were assigned in the model.
Subsequent therapy use is based on pooled FRESCO and FRESCO-2 data and patients in the BSC arm receive no subsequent anti-cancer therapies	Clinical experts at two advisory boards (UK oncologist advisory board, 22nd September 2023, and UK market access advisory board, 1st December 2023) validated pathways regarding active treatment in the considered population (47). Clinical experts advised that following BSC, patients would not receive further active treatment. Subsequent therapy proportions were included for active treatment based on proportions from the pooled FRESCO and FRESCO-2 trials. This approach aligns with the committee preferred assumptions in TA866.

Assumption	Justification
Subsequent therapy costs are assigned a one-week treatment duration	As per the committee's preferred assumptions in TA866 and TA405

Abbreviations: AE, adverse event; BSC, best supportive care; HR, hazard ratio; HRQoL, health related quality of life; PFS, progression-free survival; TA, technology appraisal; TEAE, treatment-emergent adverse event; TTD, time to treatment discontinuation; UK, United Kingdom; VEGF, vascular endothelial growth factor.

B.3.11 Base case results

As described in Section B.1.3.4, the relevant comparators for this appraisal are regorafenib, trifluridine-tipiracil, and BSC, which aligns with the NICE final scope (23). Therefore, a fully incremental analysis was conducted per the NICE reference case, comparing fruquintinib vs regorafenib, trifluridine-tipiracil, and BSC.

However, as described in Section B.3.2.8.2, feedback from clinical experts at the UK market access advisory board (1st December 2023) stated that trifluridine-tipiracil monotherapy is expected to be replaced in the near future by trifluridine-tipiracil in combination with bevacizumab (assuming a positive NICE recommendation from the ongoing appraisal ID6298), so the majority of fruquintinib use in UK clinical practice is expected to replace the use of regorafenib. Therefore, the most relevant comparison for decision making was deemed to be a pairwise comparison vs regorafenib. A pairwise comparison vs BSC is also presented to reflect the patients who have been previously treated with or are not considered candidates for trifluridine-tipiracil and/or regorafenib.

Results are based on the list prices for regorafenib and trifluridine-tipiracil, and the proposed [redacted] PAS for fruquintinib. Results based on the list price for fruquintinib are presented in Appendix R.

B.3.11.1 Base case incremental cost-effectiveness analysis results

The base case cost-effectiveness results are presented in Table 71. Fruquintinib was associated with improved mean OS (10.9 months) vs regorafenib and trifluridine-tipiracil (10.2 and 10.4 months, respectively), and improved mean PFS (4.6 months) vs regorafenib and trifluridine-tipiracil (3.4 and 3.5 months, respectively). This translated into [redacted] total QALYs for fruquintinib, yielding an incremental QALY benefit vs both regorafenib and trifluridine-tipiracil (total QALYs of [redacted] and [redacted], respectively). [redacted], net health benefit (NHB) results are also presented, in line with the NICE methods manual (138).

Fruquintinib was associated with improved mean OS (10.9 months) and improved mean PFS (4.6 months) vs BSC (7.4 months and 2.3 months, respectively). This translated into

[redacted] total QALYs for BSC, resulting in an incremental QALY benefit of [redacted] for fruquintinib vs BSC.

Based on the fully incremental analysis, BSC is the referent treatment, regorafenib is dominated by both fruquintinib and trifluridine-tipiracil, and fruquintinib is associated with an ICER of [redacted] per QALY gained vs trifluridine-tipiracil.

Critically, fruquintinib is associated with incremental QALYs of [redacted] and cost savings of [redacted] vs regorafenib and, as a result, regorafenib is dominated by fruquintinib in a pairwise comparison. In addition, fruquintinib is associated with incremental QALYs of [redacted] and incremental costs of £[redacted], resulting in an ICER of [redacted] per QALY gained vs BSC.

Pairwise NHB estimates are presented in Table 72, based on a WTP threshold of £51,000 (Section B.3.7). Fruquintinib is associated with an incremental NHB of [redacted], [redacted] and [redacted] vs BSC, trifluridine-tipiracil and regorafenib, respectively.

Appendix J presents the clinical outcomes and disaggregated results.

Table 71: Base case results (fully incremental analysis) – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 72: Base case results (Pairwise analysis) – PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (fruquintinib vs comparator) (£)	Incremental LYG (fruquintinib vs comparator)	Incremental QALYs (fruquintinib vs comparator)	Pairwise ICER (fruquintinib vs comparator)	Incremental NHB at £34,000 WTP threshold (fruquintinib vs comparator)	Incremental NHB at £51,000 WTP threshold (fruquintinib vs comparator)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	–	–	–	–	–	–

Abbreviations: BSC, best supportive care; NHB, net health benefit.

B.3.12 Exploring uncertainty

B.3.12.1 Probabilistic sensitivity analysis

A summary of the fully incremental and pairwise probabilistic results is presented in Table 73 and Table 74. Based on the fully incremental probabilistic analysis, BSC is the referent treatment, regorafenib is dominated by both fruquintinib and trifluridine-tipiracil, and fruquintinib is associated with an ICER of [redacted] per QALY gained vs trifluridine-tipiracil.

In the pairwise probabilistic analysis, fruquintinib is associated with incremental QALYs of [redacted] and cost savings of [redacted] vs regorafenib and, in line with the deterministic analysis, regorafenib is dominated by fruquintinib. In addition, fruquintinib is associated with incremental QALYs of [redacted] and incremental costs of [redacted], resulting in an ICER of [redacted] per QALY gained vs BSC.

The probabilistic fully incremental and pairwise ICERs vary slightly vs the deterministic ICERs given the sensitivity of the ICER to small differences in incremental QALYs. However, comparisons of NHB, which do not suffer from this issue, are consistent between the probabilistic and deterministic analyses. Specifically, fruquintinib was associated with incremental NHB at the £51,000 WTP threshold, of [redacted], [redacted] and [redacted] vs BSC, trifluridine-tipiracil and regorafenib respectively.

The cost-effectiveness plane for fruquintinib vs the comparators and the CEAC are presented in Figure 47 and Figure 48, respectively. Uncertainty in the probabilistic results for fruquintinib vs regorafenib and trifluridine-tipiracil arises from the confidence interval associated with the HRs applied to the fruquintinib OS and PFS curves to estimate efficacy for these comparators. Both HRs were varied independently due to the nature of a partitioned survival analysis approach, which likely overestimate the uncertainty in the model results. As shown in Section B.3.12.2, these parameters are amongst the main drivers of cost-effectiveness in the respective comparisons. The proportion of simulations considered cost-effective at a WTP threshold of £51,000 per QALY was [redacted]%.

Table 73: Base case results, probabilistic sensitivity analysis (fully incremental)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	–	–	–
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 74: Base case results, probabilistic sensitivity analysis (pairwise)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)(fruquintinib vs comparator)	Incremental QALYs (fruquintinib vs comparator)	Pairwise ICER (fruquintinib vs comparator)	Incremental NHB at £34,000 (Fruquintinib vs treatment)	Incremental NHB at £51,000 (Fruquintinib vs treatment)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, Net health benefit; QALYs, quality-adjusted life years.

Figure 47: Cost-effectiveness plane – fruquintinib PAS price

Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years.

Figure 48: Cost-effectiveness acceptability curve – fruquintinib PAS price

Abbreviations: BSC, best supportive care; WTP, willingness to pay.

B.3.12.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or ±20% of the mean value where no estimates of precision were

available. Due to the similarity in outcomes between treatments, NHB was recorded at the upper and lower values to produce a tornado diagram.

Results for the 10 most influential parameters are presented in Table 75,

Table 76, and Table 77, while the tornado diagrams are presented in Figure 49, Figure 50 and Figure 51, for comparisons against regorafenib, trifluridine-tipiracil, and BSC respectively. The most influential parameters were those associated with the OS and PFS curves for the modelled comparators vs fruquintinib, and the treatment cost of all active treatments. The NHB for fruquintinib vs regorafenib remains positive for all results other than the lower value of the OS HR applied for regorafenib. The NHB range associated with the lower and upper values of the OS HR was slightly wider for regorafenib than trifluridine-tipiracil, given the wider confidence interval for this parameter.

Table 75: OWSA results: fruquintinib vs regorafenib

Parameter	NHB at lower value of parameter	NHB at higher value of parameter
OS HR: regorafenib vs fruquintinib (FE)	[redacted]	[redacted]
Cost of pack: regorafenib	[redacted]	[redacted]
PFS HR: regorafenib vs fruquintinib (FE)	[redacted]	[redacted]
Cost of fruquintinib pack, 5mg	[redacted]	[redacted]
OS Parametric Fit (joint fits)- Parameter 3 fruquintinib- (Gen gamma Q)	[redacted]	[redacted]
TTD Parametric Fit- Parameter 1 fruquintinib- (Lognormal Meanlog)	[redacted]	[redacted]
OS Parametric Fit (joint fits) - Parameter 1 fruquintinib- (Gen gamma mu)	[redacted]	[redacted]
OS Parametric Fit (joint fits)- Parameter 2 fruquintinib- (Gen gamma sigma)	[redacted]	[redacted]
OS Parametric Fit (joint fits)- Parameter 4 fruquintinib- (Gen gamma tx predictor)	[redacted]	[redacted]
Frequency of outpatient visit	[redacted]	[redacted]

Abbreviations: FE, fixed effects; HR, hazard ratio; NHB, net health benefit; OS, overall survival; OWSA, one-way sensitivity analysis; TTD, time to treatment discontinuation.

Figure 49: Tornado diagram: fruquintinib (PAS price) vs regorafenib

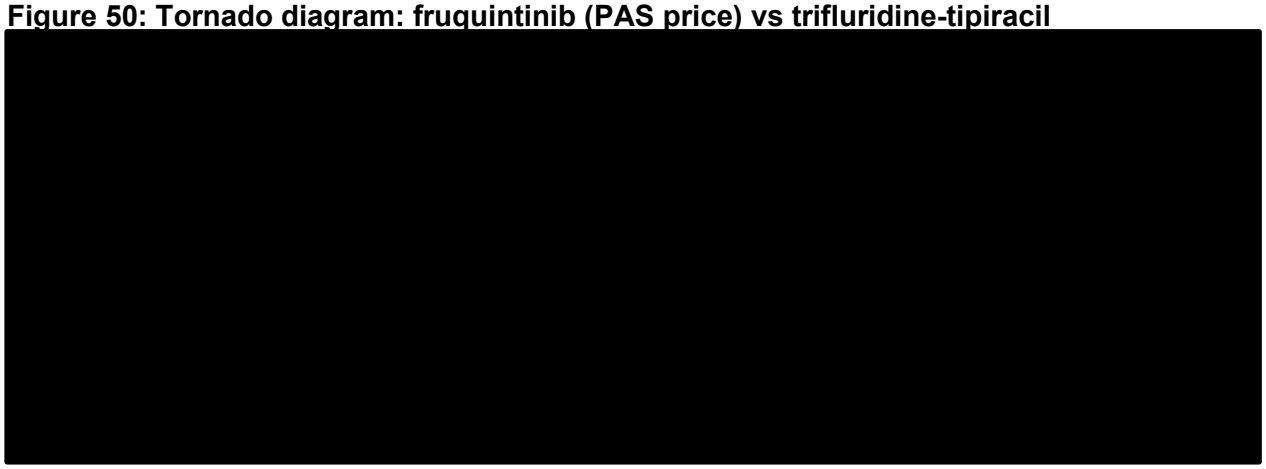
Abbreviations: FE, fixed effects; HR, hazard ratio; NHB, net health benefit; OS, overall survival; OWSA, one-way sensitivity analysis; TTD, time to treatment discontinuation

Table 76: OWSA results: fruquintinib vs trifluridine-tipiracil

Parameter	NHB at lower value of parameter	NHB at higher value of parameter
OS HR: trifluridine/tipiracil vs fruquintinib (FE)	[redacted]	[redacted]
Cost of fruquintinib pack, 5mg	[redacted]	[redacted]
PFS HR: trifluridine/tipiracil vs fruquintinib (FE)	[redacted]	[redacted]
Mean BSA	[redacted]	[redacted]
Cost of trifluridine-tipiracil pack, 20mg	[redacted]	[redacted]
Cost of trifluridine-tipiracil pack, 15mg	[redacted]	[redacted]
PFS Parametric Fit (joint fits)- parameter 3 fruquintinib- (Lognormal tx predictor)	[redacted]	[redacted]
OS Parametric Fit (joint fits) - parameter 3, fruquintinib - (Gen gamma Q)	[redacted]	[redacted]
PFS Parametric Fit (joint fits)- parameter 1 fruquintinib- (Lognormal Meanlog)	[redacted]	[redacted]
OS Parametric Fit (joint fits) - parameter 1, fruquintinib - (Gen gamma mu)	[redacted]	[redacted]

Abbreviations: BSA, body surface area; FE, fixed effects; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Figure 50: Tornado diagram: fruquintinib (PAS price) vs trifluridine-tipiracil



Abbreviations: BSA, body surface area; BSC, best supportive care; FE, fixed effects; HR, hazard ratio; PFS, progression-free survival.

Table 77: OWSA results: fruquintinib (PAS price) vs BSC

Parameter	NHB at lower value of parameter	NHB at higher value of parameter
OS Parametric Fit (joint fits)- parameter 1 fruquintinib- (Gen gamma mu)	[redacted]	[redacted]
OS Parametric Fit (joint fits)- parameter 4 fruquintinib- (Gen gamma tx predictor)	[redacted]	[redacted]
OS Parametric Fit (joint fits)- parameter 3 fruquintinib- (Gen gamma Q)	[redacted]	[redacted]
Cost of fruquintinib pack, 5mg	[redacted]	[redacted]
OS Parametric Fit (joint fits)- parameter 2 fruquintinib- (Gen gamma sigma)	[redacted]	[redacted]
PFS Parametric Fit (joint fits)- parameter 3 fruquintinib- (Lognormal tx predictor)	[redacted]	[redacted]
PFS Parametric Fit (joint fits)- parameter 1 fruquintinib- (Lognormal Meanlog)	[redacted]	[redacted]
Frequency of outpatient visit	[redacted]	[redacted]
TTD Parametric Fit- parameter 1 fruquintinib- (Lognormal Meanlog)	[redacted]	[redacted]
Utility regression model, intercept	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; HR, hazard ratio; NHB, net health benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; TTD, time to treatment discontinuation.

Figure 51: Tornado diagram: fruquintinib (PAS price) vs BSC

Abbreviations: BSC, best supportive care; HR, hazard ratio; NHB, net health benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, Progression-free survival; TTD, time to treatment discontinuation.

B.3.12.3 Scenario analysis

A summary of scenario analyses performed with justification is presented in Table 78, Table 79, Table 80, Table 81, and results of the deterministic scenario analysis are presented in Appendix Q. Probabilistic NHB estimates showed a high level of consistency with results of the deterministic analyses.

For scenario results of the comparisons of fruquintinib with regorafenib, trifluridine-tipiracil, and BSC, the NHB lay within the range of [redacted] to [redacted], [redacted] to [redacted] and [redacted] to [redacted] respectively, with most scenarios having little impact on the NHB. Fruquintinib remained dominant vs regorafenib in all of the scenarios considered. In the comparison with BSC, only four of the 29 scenarios resulted in an increase or decrease in the ICER of more than 10%. For completeness, all joint parametric models were explored in scenario analyses, however some the OS model fits were considered implausible (Section B.3.3.2.1), resulting in a relatively large impact on the NHB results for all comparators. The scenarios assuming treatment to progression for trifluridine-tipiracil and regorafenib also had a relatively large impact on the NHB for these comparisons with fruquintinib.

Table 78: Summary of scenario analyses

Base case assumption/input	Scenario analyses performed	Rationale
Discount rate 3.5% for costs and outcome	Discount rate 0% for costs and outcomes	A 3.5% discount rate was selected in line with the NICE reference case. The reference case also states that 1.5% rates may be presented alongside, therefore this is included as a scenario analysis, in addition to no discounting.
	Discount rate 1.5% for costs and outcomes	
Time horizon 10 years	Time horizon 5 years	A lifetime (10 year) time horizon was selected in line with NICE guidance. A scenario is considered in which a short-term time horizon is assessed

Base case assumption/input	Scenario analyses performed	Rationale
Fruquintinib and BSC OS modelled using joint models with the Generalised gamma distribution	Joint models with the log-logistic, log-normal, Weibull, exponential, Gompertz and gamma distributions	A joint parametric model using the generalised gamma distribution was chosen to fit the fruquintinib and BSC curves in the base case analysis. The generalised gamma distribution provides a good statistical and visual fit to the observed data, and provides long-term estimates of survival that were considered plausible by clinicians, and consistent with estimates made for BSC OS in previous appraisals, and RWE studies. Alternative joint model distributions have been considered in scenario analyses. Independent modelling using the best fitting distribution has also been considered to relax the proportional hazards assumption.
	Independent models with the log-normal distribution for fruquintinib and BSC (best fitting)	
Fruquintinib and BSC PFS modelled using joint models with the log-normal distribution	Joint models with the log-logistic, Generalised gamma, Weibull, exponential, Gompertz and gamma distributions	A joint parametric model using the log-normal distribution was chosen to fit the fruquintinib and BSC curves in the base case analysis. In line with OS and given that all PFS curves appear to have little difference with respect to visual fit, scenario analyses are performed using the other joint model distributions. Independent modelling using the best fitting distribution has also been considered to relax the proportional hazards assumption.
	Independent models with the log-normal distribution for fruquintinib and the log-logistic distribution for BSC (best fitting)	
Regorafenib and trifluridine-tipiracil TTD modelled by applying PFS HR vs fruquintinib to fruquintinib TTD	Treatment to progression assumed for all comparators	Patients are expected to discontinue treatment prior to progression based on clinical expert opinion. A scenario has been tested in which patients are treated to progression for completeness.
Concomitant medications are included in the model	Concomitant medications excluded	As per clinical expert opinion, BSC consists of concomitant medication, resource use, and palliative care. Scenario analysis removing the cost of concomitant medications aligns with the base case presented in TA866.
Subsequent therapy proportions using the pooled trial data and assuming no subsequent therapies for BSC	Subsequent therapies included for BSC	The base case assumes that patients receiving BSC do not receive subsequent therapy based on clinical opinion. Scenario analysis was performed to align the cost and efficacy data, and to align with clinical opinion that patients would receive either trifluridine-tipiracil or regorafenib, depending on the treatment they received as a primary treatment.
	Subsequent therapies based on clinical opinion	
Subsequent therapies have a one-week duration	Subsequent therapies have a two-week duration	The base case aligns with the approach taken in TA866 and TA405 and is based on survival outcomes being considered poor in subsequent lines.
Resource use estimates aligned with TA866	Resource use estimates based on clinical opinion	Base case resource use estimates are aligned with TA866. Scenario analysis is

Base case assumption/input	Scenario analyses performed	Rationale
		presented using the mean estimates from clinical experts.
Utility estimates based on the regression model from the trial	Progression decrement from TA866 applied	The progression decrement based on pooled FRESCO and FRESCO-2 data was slightly higher than in TA405 and TA866. Scenario analysis is performed to align with previous appraisals.
	Progression decrement from TA405 applied	
All Grade 1-2 AEs are associated with a 0.01 disutility	Disutility for AEs identified by clinicians as burdensome equal to the disutility for the respective Grade ≥3 AEs	UK clinicians highlighted myelosuppression, fatigue or asthenia, decreased appetite, hand-foot syndrome, and diarrhoea as the most burdensome AEs for patients treated for mCRC. Scenario analysis is performed where the disutility for Grade ≥3 AEs were applied to these Grade 1–2 AEs.

Abbreviations: BSC, best supportive care; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RWE, real world evidence; TA, technology appraisal; TTD, time to treatment discontinuation.

Table 79: Scenario analysis results vs regorafenib (probabilistic)

Scenario	Incremental costs	Incremental QALYs	Pairwise ICER (fruquintinib vs regorafenib)	Incremental NHB (fruquintinib vs regorafenib)
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 0% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 1.5% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Time Horizon 5 years	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Weibull	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Exponential	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Gamma	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Weibull	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Exponential	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Gamma	[redacted]	[redacted]	[redacted]	[redacted]
OS (individual fits: Fruquintinib and BSC) - Best fitting	[redacted]	[redacted]	[redacted]	[redacted]
PFS (individual fits: Fruquintinib and BSC) - best fitting	[redacted]	[redacted]	[redacted]	[redacted]
Treat to progression	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 AEs excluded	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments: 2 week duration	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from Pooled FRESCO and FRESCO-2	[redacted]	[redacted]	[redacted]	[redacted]
Resource use: based on clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]
Exclude concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 disutility as per Grade 3 for clinically identified AEs	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA866	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA405	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal.

Table 80: Scenario analysis results vs trifluridine-tipiracil (probabilistic)

Scenario	Incremental costs	Incremental QALYs	Pairwise ICER (fruquintinib vs trifluridine-tipiracil)	Incremental NHB (fruquintinib vs trifluridine-tipiracil)
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 0% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 1.5% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Time Horizon 5 years	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Weibull	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Exponential	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Gamma	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Weibull	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Exponential	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Gamma	[redacted]	[redacted]	[redacted]	[redacted]
OS (individual fits: Fruquintinib and BSC) - Best fitting	[redacted]	[redacted]	[redacted]	[redacted]
PFS (individual fits: Fruquintinib and BSC) - best fitting	[redacted]	[redacted]	[redacted]	[redacted]
Treat to progression	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 AEs excluded	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments: 2 week duration	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from Pooled FRESCO and FRESCO-2	[redacted]	[redacted]	[redacted]	[redacted]
Resource use: based on clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]
Exclude concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 disutility as per Grade 3 for clinically identified AEs	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA866	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA405	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal.

Table 81: Scenario analysis results vs BSC (probabilistic)

Scenario	Incremental costs	Incremental QALYs	Pairwise ICER (fruquintinib vs BSC)	Incremental NHB (fruquintinib vs BSC)
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 0% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 1.5% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Time Horizon 5 years	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - log-normal	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Weibull	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Exponential	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Gamma	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Weibull	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Exponential	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Gamma	[redacted]	[redacted]	[redacted]	[redacted]
OS (individual fits: Fruquintinib and BSC) - Best fitting	[redacted]	[redacted]	[redacted]	[redacted]
PFS (individual fits: Fruquintinib and BSC) - best fitting	[redacted]	[redacted]	[redacted]	[redacted]
Treat to progression	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 AEs excluded	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments: 2 week duration	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from Pooled FRESCO and FRESCO-2	[redacted]	[redacted]	[redacted]	[redacted]
Resource use: based on clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]
Exclude concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 disutility as per Grade 3 for clinically identified AEs	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA866	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA405	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal.

B.3.13 Subgroup analysis

No subgroup analyses are presented.

B.3.14 Benefits not captured in the QALY calculation

mCRC severely impacts patients' life expectancy as well as their HRQoL (Section B.1.3.3.2). The addition of fruquintinib to the treatment pathway would expand choice for this patient population, and the patient impact of choice is not reflected in the QALY calculation. Fruquintinib offers a favourable safety profile, and would provide a new, oral treatment option which does not negatively impact QoL, for patients unable to receive trifluridine-tipiracil or regorafenib, and for patients who have progressed on either or both of these therapies. mCRC also negatively impacts the QoL of family and caregivers of patients. Fatigue and related symptoms affect the functioning of patients with mCRC, which is associated with greater caregiver burden, and a negative impact on carers' mental and physical health, and QoL (49). Clinicians at the UK market access advisory board (1st December 2023) confirmed that fruquintinib is expected to provide another option to patients with high unmet need.

B.3.15 Validation

B.3.15.1 Validation of cost-effectiveness analysis

Assumptions and inputs used to inform the cost-effectiveness analysis were validated by leading UK clinicians and HE experts at the UK market access advisory board, as indicated throughout this appraisal. This advisory board was held on 1st December 2023 and involved four oncologists representing different centres England and Wales and three health economics experts (11).

The following topics were discussed in detail, and expert input was sought on:

- Validation of the treatment pathway and the current management of patients with mCRC
- Validation of the generalisability of the FRESCO and FRESCO-2 trials to UK clinical practice
- Validation of the approach and justification for pooling the efficacy data for fruquintinib and BSC

- Validation of clinical data sources used to inform clinical efficacy for regorafenib and trifluridine-tipiracil
- Validation of the approach to synthesising comparative efficacy for fruquintinib vs regorafenib, trifluridine-tipiracil and BSC
- Identification of prognostic and treatment effect modifiers relevant to mCRC
- Validation of the generalisability of BSC definitions across clinical trials for fruquintinib, regorafenib and trifluridine-tipiracil
- Validation of approach to survival curve extrapolations, and choice of base case distributions
- Validation of the methodology used to estimate utility values
- Validation of healthcare resource use inputs
- Proportion of patients receiving subsequent therapy by treatment arm
- The tolerability of fruquintinib compared with regorafenib and trifluridine-tipiracil
- Adverse event management for patients with mCRC and adverse events of concern
- Treatment duration of fruquintinib, regorafenib and trifluridine-tipiracil
- Validation of key assumptions.

In addition, the economic model was quality-assured through extensive quality checking processes conducted by the model developers and by four other health economists not involved in the development of the model. This was informed by the Drummond checklist (170), the Phillips checklist (171), HTA methods guides (138, 172-174) and NICE DSU TSD series, and included cell-by-cell checks, extreme value testing and logical checks, as well as a rebuild of the model engine.

B.3.15.2 Comparison with trial outcomes

Model outcomes for fruquintinib and BSC were compared to the pooled clinical trial data. Figure 52 and Figure 53 compare the pooled FRESCO and FRESCO-2 KM data with the associated parametric extrapolations for OS and PFS during the trial period, respectively. Landmark estimates for 3–18 months and median survival are compared in Table 82. The base case extrapolations for fruquintinib and BSC were closely aligned with the pooled

FRESCO and FRESCO-2 data throughout the trial period. There is some minor variation, as expected when applying a smoothed curve to a stepped KM function, and there is more variation towards the end of the KM curve, where fewer patient remain at risk. However, at all-time points presented, the predicted curve is within 4% of the trial data, with the exception of BSC PFS, in which there is a significant drop off in the number of patients at risk within the first 2 months, with the number at risk falling from 368 to 190 in the first 8 weeks. Overall, due to the maturity of the available KM data (discussed in Section B.2.6.3), the base case survival curves provide a good fit to the trial data.

Figure 52: Pooled KM data comparison with survival curves, trial period, OS, joint models

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival.

Figure 53: Pooled KM data comparison with survival curves, trial period, PFS, joint models

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival.

Table 82: Model comparison with trial outcomes

Outcome	Source	Median (months)	3 months	6 months	9 months	12 months	15 months	18 months
Fruquintinib								
OS (generalised gamma distribution, joint model)	Pooled trial data	8.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (log-normal distribution, joint model)	Pooled trial data	3.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC								
OS (generalised gamma distribution, joint model)	Pooled trial data	5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (log-normal distribution, joint model)	Pooled trial data	1.6	[redacted]	[redacted]	[redacted]	–	–	–
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival.

B.3.15.3 External validity

Model outcomes for fruquintinib, regorafenib, trifluridine-tipiracil and BSC were compared with observed outcomes of key comparator trials and RWE identified by the clinical SLR (Appendix D), and published evidence in previous NICE appraisals where available.

For all comparators, the predicted median OS and PFS align with reported medians in the literature.

- For fruquintinib, the modelled median OS and PFS ([redacted] months and [redacted] months, respectively) are comparable to the observed data from key RCTs, which range from 7.4–9.3 months and 3.7–4.7 months, respectively, and the fruquintinib RWE studies identified in the clinical SLR (Appendix D, Section D.2.4), which range from which range from 7.5–11.3 months and 3–6.7 months, respectively.

- For regorafenib, predicted median OS ([redacted]months) is similar to the model predicted value used for decision making in TA866 (7.1 months), is within 0.7 months of the pooled CORRECT and CONCUR data (6.9 months), and is well aligned with RWE (5.6-7.7 months). Predicted median PFS (2.8 months) is the same as the pooled CORRECT and CONCUR data (2.8 months) in TA866 and is well aligned with the data reported from the RWE (2.7-3.1 months).

- For trifluridine-tipiracil, predicted median OS ([redacted] months) is comparable to observed outcomes in the RECOURSE and TERRA RCTs (7.2 and 7.8 months, respectively) and predicted outcomes in TA405 (7.4 months), as well as RWE (5.8-7.6 months). Similarly, the predicted median PFS (2.8 months) is aligned with the predicted outcomes in TA405 (2.9 months), as well as the data from the RCTs and RWE studies (2.0-3.3 months).

- For BSC, the predicted median OS ([redacted] months) is well aligned with the literature, for example, the pooled CORRECT and CONCUR data (5.3 months) and the pooled RECOURSE and Yoshino data (5.4 months) used to inform the TA866 and TA405 clinical data, respectively, and is well aligned with the observed data from key RCTs, which range from 4.8–6.6 months.

Table 83: Median OS and PFS comparisons, regorafenib, trifluridine-tipiracil and BSC

Distribution	Median OS (months)	Median PFS (months)
Fruquintinib		
FRESCO (83)	9.3	3.7
FRESCO-2 (63)	7.4	3.7
Xu, 2012 (95)	7.7	4.7
Pooled FRESCO and FRESCO-2 (116)	8.0	3.7
Predicted by the economic model	[redacted]	[redacted]
Regorafenib		
CORRECT (10)	6.4	1.9
CONCUR(102)	8.8	3.2
TA866 model predicted value (7)	7.1	2.8
Pooled CORRECT and CONCUR (10)	6.9	2.1
REBECCA RWE study (144)	5.6	2.7
CORRELATE RWE study (41)	7.7	2.9
RECORA RWE study (45)	5.8	3.1
Predicted by the economic model	[redacted]	[redacted]
Trifluridine-tipiracil		
RECOURSE (9)	7.2	2.0
TERRA (175)	7.8	2.0
Yoshino (110)	9.0	2.0
TA405 model predicted value (55)	7.4	2.9
Pooled RECOURSE and Yoshino (55)	7.3	1.9
Tong RWE study (145)	5.8	3.2
Stavraka RWE study (62)	7.6	3.3
Predicted by the economic model	[redacted]	[redacted]
BSC		
FRESCO (83)	6.6	1.8
FRESCO-2 (63)	4.8	1.8
Xu, 2012 (95)	5.5	1.0
CORRECT(10)	5.0	1.7
CONCUR(102)	6.3	1.7
Pooled CORRECT and CONCUR (10)	5.3	1.8
TA405 model predicted value	5.3	1.6
RECOURSE (9)	5.2	1.7
TERRA (175)	7.1	1.8
Yoshino (110)	6.6	1.0
Pooled RECOURSE and Yoshino (55)	5.4	1.7
Predicted by the economic model	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival.

B.3.16 Interpretation and conclusions of economic evidence

B.3.16.1 Conclusions

Feedback from clinical experts at the UK market access advisory board (1st December 2023) advised that trifluridine-tipiracil monotherapy is expected to be replaced in the near future by trifluridine-tipiracil in combination with bevacizumab (subject to positive NICE guidance from the ongoing appraisal ID6298), so the majority of fruquintinib use in UK clinical practice is expected to replace regorafenib. Therefore, the most relevant comparison for decision making was deemed to be vs regorafenib. At the proposed PAS price, fruquintinib dominated regorafenib (less costly and more effective). A pairwise comparison vs BSC is also relevant for patients who have been previously treated with or are not considered candidates for trifluridine-tipiracil and/or regorafenib. In this comparison, fruquintinib generated incremental QALYs of [redacted] and incremental costs of [redacted], resulting in an ICER of [redacted] per QALY gained vs BSC.

The fully incremental cost-effectiveness analysis estimated that fruquintinib is associated with incremental costs of [redacted] and incremental QALYs of [redacted] vs trifluridine-tipiracil, with an ICER of [redacted]. The QALY gain for fruquintinib is driven by improved mean OS and mean PFS vs all modelled comparators, as highlighted in the NMA results (Section B.2.9.5).

Results were found to be robust in one-way sensitivity analysis (OWSA) and in a series of scenario analyses where model assumptions were tested. Fruquintinib was dominant vs regorafenib in all scenario analyses and all but one OWSA result.

At a WTP threshold of £51,000 per QALY, the NHB associated with fruquintinib was [redacted] and [redacted] vs regorafenib, trifluridine-tipiracil, and BSC, respectively. Deterministic base case NHB estimates were highly consistent with the probabilistic NHB ([redacted], [redacted] and [redacted] vs regorafenib, trifluridine-tipiracil, and BSC, respectively).

QALY shortfall calculations suggest a severity modifier of 1.7 is appropriate for all comparisons in this analysis, given that proportional QALY shortfall was estimated to be 0.96, 0.96, and 0.97 for regorafenib, trifluridine-tipiracil, and BSC, respectively. Critically, in all scenario analyses conducted which influence QALY estimates, the severity modifier remains 1.7 vs all comparators, demonstrating the robustness of the severity modifier estimates to changing assumptions.

B.3.16.2 Strengths and weaknesses

A *de novo* health economic model was developed to assess the cost-effectiveness of fruquintinib vs regorafenib, trifluridine-tipiracil and BSC in [redacted] The model structure was consistent with previous HTAs in mCRC, including the trifluridine-tipiracil (TA405) and regorafenib (TA866) NICE appraisals.

Key model inputs, including clinical efficacy estimates for fruquintinib and BSC, were informed by the pooled FRESCO and FRESCO-2 data, thereby leveraging both large, blinded, Phase III RCTs that assessed fruquintinib vs BSC in the population of interest to maximise the sample size of the analysis. This was considered the best use of the available evidence by experts at a UK market access advisory board (1st December 2023) (11), as the pooled population is more generalisable to the UK patient population vs using the studies independently, and hence is most relevant for decision-making.

In addition, the pooled OS and PFS data for fruquintinib and BSC were mature (68.3% and 76.6% of patients experienced an OS event, respectively) hence limited extrapolation of OS and PFS was required. This resulted in the majority of parametric models providing good visual and statistical fit to the data, and similar extrapolations across candidate distributions. Importantly, modelled outcomes predicted an OS and PFS benefit with fruquintinib vs regorafenib, trifluridine-tipiracil and BSC. Changes in survival extrapolations were explored in scenario analyses, however this resulted in immaterial changes to cost-effectiveness estimates.

HRQoL data from FRESCO-2 were used to inform utility, leveraging data from a global Phase III RCT in the population of interest, that represents a large patient population (N=691). The multivariable mixed-effects repeated-measures regression model was validated by clinical and health economic experts at a UK market access advisory board (1st December 2023) (11), and estimated progression-free health state utility values were comparable to those accepted in TA405 and TA866 (7, 55). Given the number of post-progression observations in the FRESCO-2 data (213 and 113 observations in the fruquintinib and BSC arms, respectively), scenarios were explored where the progressed disease vs progression-free utility decrements reported in TA405 and TA866 were applied to the progression-free utility value derived from FRESCO-2. These scenario analyses did not

yield material changes in cost-effectiveness estimates, indicating this is not a source of decision uncertainty.

Moreover, the inputs, methods and assumptions used to inform the analysis were validated by UK clinicians and health economics experts at the UK market access advisory board UK market access advisory board (1st December 2023) (11). Extrapolated PFS and OS for fruquintinib, regorafenib, trifluridine-tipiracil aligned with clinical expert opinion, observed data from the relevant key clinical trials, RWE identified by the clinical SLR, and data reported in prior HTAs in mCRC. Uncertainty in assumptions and inputs were explored in a series of scenario analyses which demonstrated the robustness of results.

A key limitation of the analysis was the lack of head-to-head data comparing fruquintinib to regorafenib and trifluridine-tipiracil. Therefore, an NMA was conducted to synthesise relative treatment effects for OS and PFS. Uncertainty in the analysis was explored via a series of extensive scenario analyses that yielded highly consistent results, supporting the minimal impact of heterogeneity on results. Results of the NMA (fruquintinib, regorafenib and trifluridine-tipiracil vs BSC) were consistent with the observed data reported in key clinical trials contributing to the analysis and outcomes of the NMA presented in TA866, and so were considered robust. Predicted median OS and PFS for regorafenib, trifluridine-tipiracil and BSC were consistent with the observed data reported in the literature from the key clinical trials, the predicted outcomes in TA405 and TA866, and RWE identified by the clinical SLR.

Overall, a positive NICE recommendation for fruquintinib would provide patients and clinicians with a convenient, alternative, oral treatment option with a manageable safety profile, which does not negatively impact quality-of-life, for patients with previously treated mCRC.

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Appendices

- Appendix C: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Subgroup analysis
- Appendix F: Adverse reactions
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Summary of Information for Patients (SIP)

February 2024

File name	Version	Contains confidential information	Date
ID6274-Fruquintinib-PrevTreatedmCRC-SIP.docx	1	No	14 February 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic: Fruquintinib Brand name: Fruzaqla™

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Fruquintinib is intended to be used by adult patients with colorectal cancer (CRC) which has spread to other parts of the body (metastatic). It is used when other treatments have not worked or when other treatments are not suitable. These treatments include fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Fruquintinib does not currently have a marketing authorisation in the United Kingdom (UK). Regulatory approval by the Medicines and Healthcare products Regulatory Agency (MHRA) is ongoing and a decision is expected later in 2024 (Document B, Section B.1.2, Table 2).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine.

Please outline the reason and purpose for the engagement/activity and any financial support provided:

Takeda is in the process of providing a hands-off donation to Bowel Cancer UK, following a request to provide funding to support their core operations.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Colorectal cancer (CRC) is a group of diseases with distinctive genetic differences (1). About two-thirds of new cases of CRC are found in the colon, and about one-third in the rectum (2). In the UK, CRC is the third most commonly diagnosed cancer (3). Around 34,400 new cases of CRC are diagnosed each year in England, making up 12% of all new cancer diagnoses (4). In 2020, 22% of CRC cases in England were diagnosed at the most advanced state, Stage IV (5), which means the cancer has spread to other sites in the body ("metastasised"). Additionally, around 55% of patients with earlier stage disease will develop metastatic disease (6). This means that overall, there are around 17,000 new cases of metastatic CRC (mCRC) each year in England (4-6). The exact cause of CRC is unknown but factors which may increase a person's risk of developing CRC over their lifetime include older age (7, 8), male sex (8), family history of CRC (9), and lifestyle factors such as high consumption of red and processed meat, obesity, diabetes, and excessive consumption of alcohol, and smoking (9). In the UK, CRC is the second most common cause of cancer-related deaths (3). Long-term survival will vary, depending on stage of disease at diagnosis (see Section 2b) and worsens considerably if patients develop metastatic disease. In England, 91% of patients diagnosed with the earliest stage of disease (Stage I), are alive 5 years after diagnosis. Only 11% of patients diagnosed with Stage IV disease are alive 5 years after diagnosis (5). When newly diagnosed mCRC patients are treated in line with European guidelines, the average survival time is 30 months (10), but this diminishes with each subsequent treatment that fails to work. In patients who have received two or more previous treatments, average survival time is only 5–7 months (11, 12). For patients receiving their first treatment, progression-free survival (the time before disease worsens) is 8.5 months (13). This decreases to only 2 months for patients who have received two or more previous treatments (11, 14). Patients with mCRC experience burdensome symptoms such as fatigue, nausea, altered bowel habits, abdominal pain, rectal bleeding, and microcytic anaemia (a blood disorder where the red blood cells are too small to carry sufficient oxygen) (15). Patients with liver metastases may also experience jaundice and ascites (collection of fluid in the abdomen) (16). Patients can also experience side effects from their cancer treatment such as fatigue, nausea, neuropathy (nerve damage that leads to pain, weakness, numbness or tingling in one or more parts of the body), impaired cognitive functioning (reduced ability to pay attention, think,

understand, learn, or remember), and symptoms of myelosuppression (reduction in blood cell production by the bone marrow) (11, 15). Myelosuppression may result in a lack of red blood cells (anaemia; can lead to tiredness and shortness of breath), white blood cells (leukopenia and neutropenia; can increase risk of developing infections) and platelets (thrombocytopenia; can increase risk of bleeding). To resolve myelosuppression, a patient's treatment may need to be delayed, be given at a lower dose, or stopped completely – which could reduce how well the treatment works against the patient's cancer. For patients with mCRC who have undergone two or more previous treatments (the target population for fruquintinib), existing treatment options often come with side effects that patients may find burdensome (11, 14).

All these disease-related symptoms and treatment side effects can severely impact a patient's quality of life (15). Patients with CRC can show significantly high levels of psychological distress, with up to 57% of patients suffering from depression and up to 47% of patients suffering from anxiety (17).

The quality of life of family and caregivers of patients with CRC are also negatively impacted. Fatigue and related symptoms affect the functioning of patients with CRC, meaning they may become highly dependent on formal or informal caregivers. This can affect carers' mental and physical health, and quality of life (18).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

In England, the National Health Service (NHS) Bowel Cancer Screening Programme means a screening test is automatically sent every 2 years to people who are aged 60–74 years and registered with a general practitioner (GP) (19, 20). The programme is expanding to include everyone aged 50 to 59 years. This screening programme aims to diagnose the disease at the earliest stage possible, where survival outcomes are best, to prevent as many patients as possible being diagnosed with Stage IV at the outset.

For patients with symptoms, or those with an abnormal screening test through the NHS Bowel Cancer Screening Programme, CRC will be diagnosed based on results from:

- stool tests
- blood tests
- diagnostic colonoscopy (a medical procedure in which a flexible fibre-optic instrument is inserted through the anus in order to examine the colon) or proctoscopy (an examination of the rectum and anal cavity with a proctoscope [a hollow tube, usually with a tiny light at the end])
- biopsy (a procedure to remove cells, tissue or fluid for medical examination) (21).

After diagnosis of CRC, the tumour will be staged based on where the tumour is located and where it has spread (22):

- Stage 0 – There are cancer cells in the bowel lining, but they are completely contained. There is little risk of any cancer cells having spread
- Stage I – The cancer has grown through the inner lining of the bowel, or into the muscle wall. It has not spread to lymph nodes or distant body parts
- Stage II – The cancer has spread into the outer wall of the bowel or into tissue or organs next to the bowel. It has not spread to the lymph nodes or distant parts of the body
- Stage III – The cancer has spread to nearby lymph nodes but has not spread to distant body parts

- Stage IV – The cancer has spread to other sites in the body (metastasised).

Despite the Bowel Cancer Screening Programme, almost half of patients are diagnosed at, or progress to Stage IV. Around 85% of these patients have tumours that cannot be removed by surgery, and therefore cannot be cured. However, there are a number of treatment options to control the cancer for as long as possible (see Section 2c).

No additional tests beyond the usual diagnostic procedures are required for treatment with fruquintinib.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

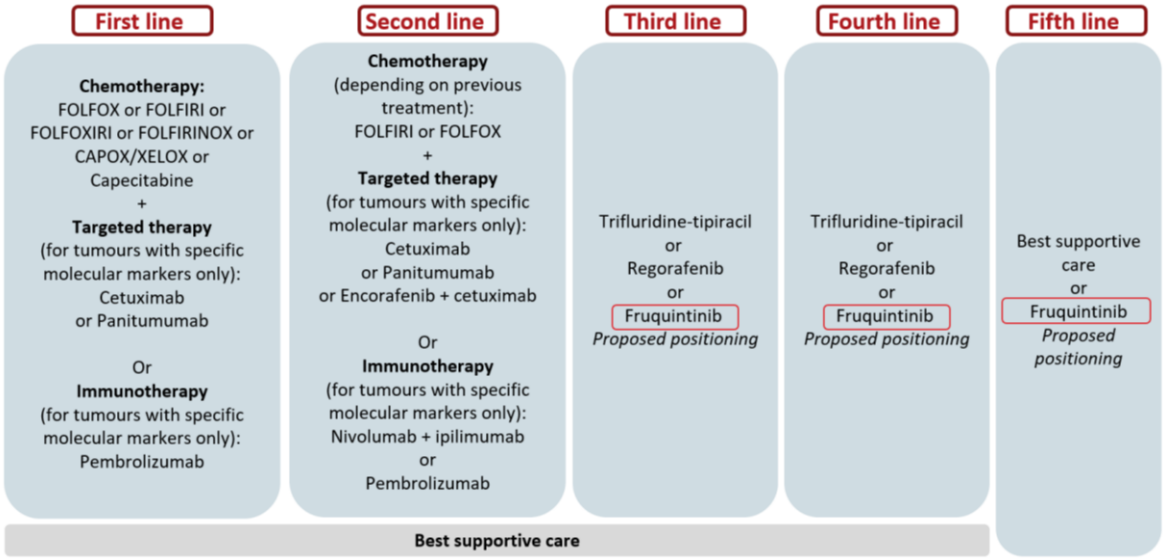
For patients with incurable mCRC, the main aim of treatment is to prolong survival while maintaining the best possible quality of life (12). Most patients will receive treatment for the remainder of their lives.

In order to determine the most effective first treatment, the cancer is analysed at a molecular level. Most patients will receive chemotherapy, and those with molecular markers (naturally occurring molecules, genes, or other characteristics by which a particular physiological process or disease can be identified) may receive an additional targeted therapy. A small proportion of patients with specific molecular markers may receive immunotherapy only. If this first treatment stops working, the next treatment choice depends on the types of previous treatments received, the fitness of the patient, and the likelihood of tolerating the side effects from further treatment (23, 24).

Fruquintinib is expected to be used by patients with mCRC who have already been treated with two or more previous treatments (Figure 1). At this time , patients are likely to be experiencing a large burden from their disease and treatment, with a poor prognosis.

Currently, there are two active treatments that can be prescribed for patients in this setting: regorafenib (Stivarga™) and trifluridine with tipiracil (trifluridine-tipiracil; Lonsurf™) (25, 26).

Figure 1: Future anticipated treatment pathway for mCRC with fruquintinib



Sources: Grothey et al, 2021 (27), Van Cutsem et al, 2016 (10), NICE TA709 (28), NICE TA439 (29), NICE TA716 (30), NICE TA668 (31), NICE TA61 (32), TA405 (33), NICE TA866 (26), NICE TA914 (34).
Abbreviations: CAPOX/XELOX, capecitabine and oxaliplatin; FOLFIRINOX, fluorouracil, irinotecan and oxaliplatin; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; mCRC, metastatic colorectal cancer.

Regorafenib is a vascular endothelial growth factor receptor (VEGFR) inhibitor like fruquintinib (please see Section 3a). However, unlike fruquintinib, regorafenib inhibits other receptors as well (35, 36), which may lead to patients experiencing more side effects. The most common reasons for patients discontinuing treatment with regorafenib are side effects such as fatigue and hand-foot syndrome (14, 23). Trifluridine-tipiracil is a combination chemotherapy treatment (37). Trifluridine-tipiracil is associated with high rates of myelosuppression, which can result in treatment delays and interruptions, and an increased risk of infection and hospitalisation (11, 23).

If approved, fruquintinib would either be used as an alternative to trifluridine-tipiracil and/or regorafenib, or after these treatments. Fruquintinib would also be used by patients who cannot tolerate or who are contraindicated (patients for whom the drug may be harmful) to trifluridine-tipiracil and/or regorafenib. Currently, the only option for those patients is to receive best supportive care (BSC) alone. In some settings, BSC may be known as palliative care and means a patient's cancer is no longer being actively treated, but instead they are receiving care to manage the symptoms and complications of the disease.

In patients with previously treated mCRC, there is a need for alternative options that are effective, well-tolerated, and which do not adversely impact their quality of life. Takeda has received advice from a group of consultant oncologists who treat CRC in the UK, who advised that fruquintinib would provide a viable choice for patients facing high unmet needs, potentially offering improved outcomes and a better quality of life.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers

and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patient-reported outcomes, which included questionnaires to capture detail on a patient's quality of life, were included in one of the clinical trials investigating fruquintinib (known as FRESCO-2, described in Section 3f). Collection of further patient-based evidence for mCRC is ongoing by Takeda, and aims to include patients from the UK.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

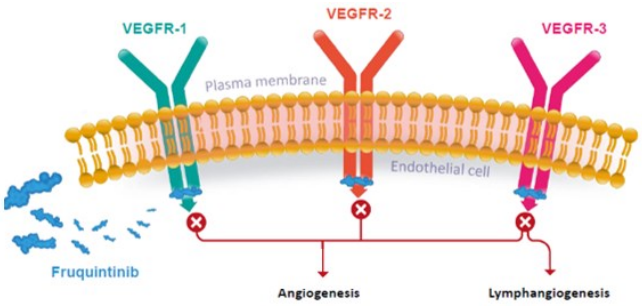
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Vascular endothelial growth factor (VEGF) is a protein that is produced and released by various cells in the body. It stimulates the formation of blood vessels by binding to VEGF receptors (VEGFR) expressed on other tissues in the body. These receptors are typically found on the surface of blood vessels, including those close to the tumour. When CRC tumour cells release VEGF, it binds to nearby VEGFR (Figure 1), encouraging the growth of new blood vessels (angiogenesis) which provide oxygen and nutrients to the tumour and support tumour growth (38, 39). A cancer treatment involving a VEGF inhibitor therefore targets the VEGF protein to prevent its interaction with VEGFR, whereas a VEGFR inhibitor directly hinders the receptors' activation by VEGF. Both approaches aim to disrupt angiogenesis, impacting blood vessel formation and potentially inhibiting tumour growth (38).

There are three different VEGFRs involved in the growth of blood vessels. Fruquintinib is a highly selective and potent inhibitor of all three VEGFRs (Figure 2) and has little effect on other receptors in the cell. As fruquintinib is highly selective for VEGFRs, it is expected to limit tumour growth while minimising the side effects patients may experience. Fruquintinib also has the potential to inhibit the growth of lymphatic vessels (lymphangiogenesis). Other VEGF/VEGFR inhibitors used to treat mCRC are not as selective as fruquintinib, as they target other receptors, meaning patients may experience more side effects (40, 41).

Figure 2: Inhibition of VEGFRs by fruquintinib



Source: Geindreau et al, 2021 (38), Qin et al, 2019 (39) Zhang et al, 2019 (41).
Abbreviations: VEGFR, vascular endothelial growth factor receptor.

Overall, fruquintinib works selectively against a mCRC disease to address the unmet needs of patients with previously treated mCRC (40, 41).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

In the indication of interest to this NICE appraisal, fruquintinib is not intended to be used as a combination therapy.

However, it is expected that fruquintinib will be used alongside BSC to manage symptoms and complications of their disease. These are treatments used to manage the symptoms of disease, rather than the disease itself.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose of fruquintinib is 5 mg (one 5 mg capsule) once a day, at approximately the same time each day. The dose is taken for 21 consecutive days, followed by a 7 day break. Similarly to regorafenib and trifluridine-tipiracil, fruquintinib is taken orally and therefore, patients do not need to attend hospital to receive their medicine.

For patients experiencing side effects, the dose should be reduced; 1 mg capsules for this. The first dose reduction is to 4 mg once a day. If the patient continues to experience side effects, the

second dose reduction is to 3 mg once a day. Fruquintinib should be permanently discontinued in patients who are not able to tolerate a dose of 3 mg once a day.

Treatment with fruquintinib should be continued until disease progression or unacceptable toxicity occurs. This should be decided by the doctor, in consultation with the patient.

Unlike regorafenib or trifluridine-tipiracil, fruquintinib is taken only once a day. Regorafenib is administered at a dose of 160 mg (4 x 40 mg tablets) once a day for 3 weeks followed by 1 week off therapy (35). Trifluridine-tipiracil (35 mg/m^2 – the dose is calculated based on the surface area of a patient's body) is taken twice a day for 5 days a week, followed by a 2-day break, for 2 weeks. This is then followed by a 14-day break (37).

Furthermore, fruquintinib can be taken with or without food. This compares favourably with regorafenib which is recommended to be taken with a low-fat meal, and trifluridine-tipiracil which is to be taken with food (35, 37).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The key clinical trials providing evidence for fruquintinib in mCRC are two completed Phase 3 trials called FRESCO and FRESCO-2 (42, 43). In both studies, patients received fruquintinib oral capsules at a dose of 5 mg once a day, the same dose expected to be used by patients if approved for use on the NHS. Evidence from the FRESCO and FRESCO-2 trials has been published in peer-reviewed journals (42, 43).

FRESCO (NCT02314819) – https://jamanetwork.com/journals/jama/fullarticle/2685988

The FRESCO trial was a randomised (meaning people were allocated at random to one of two groups, either fruquintinib or placebo), double-blind (neither patients nor trial organisers knew which treatment was allocated), placebo-controlled (fruquintinib was compared with a placebo), multicentre (conducted at more than one medical centre), Phase 3 study (trial comparing a new treatment with the standard treatment or a placebo) in adults with mCRC who had tumour progression following chemotherapy regimens that included fluoropyrimidine, oxaliplatin, and irinotecan (42). FRESCO was conducted across 28 centres in China and completed in January 2017. People could take part if they (42):

- Were adults with Stage IV CRC
- Had previously received and failed on at least two lines of standard fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. Prior treatment with VEGF and/or EGFR inhibitors was permitted.

Patients were randomised to either fruquintinib or placebo. Patients received fruquintinib or placebo, both in addition to BSC. Patients treated with fruquintinib received 5 mg once a day, orally, for 3 weeks (42). This was followed by 1 week without treatment with fruquintinib. Patients treated with placebo received 5 mg placebo capsules once a day, orally for 3 weeks (42). This was followed by 1 week without treatment with placebo. Each treatment cycle lasted for 28 days. A total of 416 patients took part in FRESCO (278 treated with fruquintinib, and 138 treated with placebo) (42).

FRESCO-2 (NCT04322539) – https://www.thelancet.com/article/S0140-6736(23)00772-9/fulltext

The FRESCO-2 trial was a randomised, double-blind, placebo-controlled, multicentre, Phase 3 study in adults with refractory mCRC who had progressed on or been intolerant to treatment with chemotherapy, biological therapy and either trifluridine-tipiracil or regorafenib (43). FRESCO-2 enrolled patients across 124 centres in Australia, Europe, Japan, and the US and completed in July 2022 (43). There were three centres in the UK, which enrolled three patients. People could take part if they (43):

- Were adults with Stage IV (metastatic) CRC
- Had progressed on or were intolerant to treatment with trifluridine-tipiracil and/or regorafenib, and had previously been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, a VEGF inhibitor and if eligible, a targeted therapy.

Patients were randomised to either fruquintinib or placebo. Patients received fruquintinib or placebo, both in addition to BSC. Patients in FRESCO-2 received the same dosing regimen for fruquintinib and placebo as patients in FRESCO (42, 43). A total of 691 patients took part in FRESCO-2 (461 treated with fruquintinib, and 230 treated with placebo).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Efficacy evidence for fruquintinib from FRESCO and FRESCO-2

Overall survival (how long a patient survives) – Document B, Section B.2.6.2.1

In both FRESCO and FRESCO-2 studies (42, 43), fruquintinib showed significant improvements in how long patients survived compared with placebo. The improvement in overall survival is considered clinically meaningful, particularly in this later line setting where outcomes are poor.

In FRESCO, people taking fruquintinib lived for an average of 9.3 months, which is 2.7 months longer than those taking the placebo (who lived for an average of 6.6 months) (42). The risk of dying was 35% lower with fruquintinib compared with placebo (42).

In FRESCO-2, results were similar. People taking fruquintinib lived for an average of 7.4 months, which is 2.6 months longer than those taking the placebo (who lived for an average of 4.8 months) (43). The risk of dying was 34% lower with fruquintinib compared with placebo (43).

In a study looking at treatment preferences in patients with mCRC, overall survival was found to be the most important factor behind patients' choice of treatment (44).

Progression-free survival (how long before a patient's disease worsens) – Document B, Section B.2.6.2.2.1

In both FRESCO and FRESCO-2, fruquintinib showed significant improvements in how long patients lived before their disease worsened compared with placebo (42, 43).

FRESCO found that for those receiving fruquintinib, progression-free survival was 1.9 months longer compared with those receiving placebo (3.7 months with fruquintinib versus 1.8 months

with placebo) (42). The risk of the disease getting worse, or death was 74% lower for those on fruquintinib compared with placebo (42).

FRESCO-2 found that progression-free survival was 1.9 months longer for those receiving fruquintinib compared with those receiving placebo (3.7 months with fruquintinib versus 1.8 months with placebo) (43). The risk of the disease getting worse, or death was 68% lower for those on fruquintinib compared with placebo (43).

Disease control rate (how much a drug works against the disease, or stops it from getting worse) – Document B, Section B.2.6.2.2.2

In both FRESCO and FRESCO-2, fruquintinib showed a significant improvement compared with placebo in how much it worked against the disease, or stopped it from getting worse (42, 43).

In FRESCO, 62.2% of the people taking fruquintinib had their disease under control compared with 12.3% on placebo (42). Similarly, in FRESCO-2, 55.5% of people on fruquintinib had their disease under control compared with 16.1% on placebo (43).

Efficacy evidence for fruquintinib using combined data from FRESCO and FRESCO-2 – Document B, Section B.2.6.3

For the purposes of the NICE submission, the FRESCO and FRESCO-2 clinical trial data were combined to best represent patients in the UK expected to be treated with fruquintinib. In this combined analysis of FRESCO and FRESCO-2, fruquintinib showed consistent and significant benefits for patients. The results showed that fruquintinib extended the time patients lived and also significantly delayed disease progression compared with placebo.

Clinical effectiveness data for fruquintinib in comparison with existing treatments – Document B, Section B.2.9

There is no direct evidence to show the effectiveness of fruquintinib compared with regorafenib and trifluridine-tipiracil. To generate evidence, a type of statistical analysis known as a network meta-analysis was conducted. This estimated how well fruquintinib works compared with these treatments. The results showed that fruquintinib significantly reduced the risk of the disease getting worse compared with both trifluridine-tipiracil and regorafenib. The analysis also showed that treatment with fruquintinib achieves benefits consistent with trifluridine-tipiracil and regorafenib for overall survival.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patients with mCRC experience worse quality of life with each additional line of therapy they receive (45). It is important that the treatment a patient receives does not further worsen their quality of life.

Quality of life was measured in FRESCO-2 using two different measures, which were completed by patients before starting treatment and on the first day of each treatment cycle:

- **EQ-5D-5L:** This is a questionnaire looking at five areas relating to health – how easily you move around, take care of yourself, handle daily activities, deal with pain or discomfort, and manage feelings of anxiety or depression. It helps to assess how the treatment influences different parts of patients' daily lives
- **European Organisation for the Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30):** This is a cancer-specific questionnaire that measures patients' physical health, psychological, and social function.

At the beginning of FRESCO-2, scores were similar between patients receiving fruquintinib and those receiving placebo (43). Over time, patients receiving fruquintinib showed a slower decline in quality of life compared with those receiving placebo (43). Patients on fruquintinib did not experience a worsening of their disease as rapidly as those on placebo (43). When comparing score changes, results showed that patients receiving fruquintinib appear to fare better in overall wellbeing compared with placebo (43). Results also indicated that fruquintinib might delay the decline in quality of life compared with placebo.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In both the FRESCO and FRESCO-2 trials, fruquintinib was generally well tolerated. Between 15 and 20% of patients stopped treatment and around 24% of patients had to receive a lower dose due to side effects. Patients who received fruquintinib stayed on treatment for 4–5 months, twice as long as those who received placebo (2 months).

In both trials the majority of adverse events (side effects) were moderate and manageable. The most frequently reported adverse events by patients treated with fruquintinib were hypertension (high blood pressure; FRESCO: 57%, FRESCO-2: 37%), hand-foot syndrome (redness, swelling, and pain on the palms of the hands and/or the soles of the feet; FRESCO: 49%, FRESCO-2: 19%), proteinuria (the presence of excess protein in the urine; FRESCO: 43%, FRESCO-2: 17%). Hypertension and hand-foot syndrome are known side effects of VEGFR inhibitors; hypertension can easily be treated by the patient's GP practice and hand-foot syndrome with topical ointment. The most frequently reported adverse events by patients treated with placebo were proteinuria (FRESCO: 25%, FRESCO-2: 5%), elevated aspartate aminotransferase (a liver enzyme; FRESCO: 18%, FRESCO-2: 5%) and hypertension (FRESCO: 15%, FRESCO-2: 5%).

With its manageable safety profile, fruquintinib provides an alternative treatment option for patients who are unable to tolerate trifluridine-tipiracil and/or regorafenib.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Fruquintinib may expand the choice of treatments available to patients who have had two or more lines of therapy. Fruquintinib has the potential to offer patients with a high unmet need an oral treatment option that extends life (overall survival) by around 2.5 months (versus placebo), with a slower decline in quality of life, therefore providing patients with more valuable time with family and friends. Its unique mechanism of action also means that fruquintinib offers patients manageable side effects, therefore the treatment is easier for patients to handle, versus other available treatments, and potentially reducing the overall burden on their health.

Patients eligible for treatment with fruquintinib (patients who have had two or more previous treatments) would be facing limited treatment options, and a poor prognosis. Fruquintinib could therefore offer another active treatment option and potentially delay the time to when patients would have to move to receiving just best supportive care.

Fruquintinib is a treatment that targets specific VEGF receptors involved in blood vessel growth (angiogenesis) (41). It focuses on all three VEGF receptors with high specificity (41), as shown in Figure 2 in Section 3a. This targeted approach of fruquintinib may help slow down the formation of new blood vessels and lymphatic vessels to the tumour and slow tumour growth (41). Unlike some other treatments for mCRC, fruquintinib has minimal effects on other receptors, potentially causing fewer side effects for patients (41).

The results of clinical trials, FRESCO (42), FRESCO-2 (43), and the combined analysis (FRESCO + FRESCO-2) show that fruquintinib extends overall survival and progression-free survival, and improves disease control rate compared with placebo. They also show that fruquintinib provides a manageable safety and tolerability profile (see Section 3g).

Studies assessing how well fruquintinib performs in the real world (not just in controlled trials), show that overall survival and progression-free survival, when treated with fruquintinib, are similar to results in controlled trials (46-50). An indirect comparison also showed that fruquintinib has a slightly lower risk of the disease getting worse compared with both trifluridine-tipiracil and regorafenib, and that fruquintinib works similarly well to regorafenib and trifluridine-tipiracil in terms of overall survival (see Section 3e).

As discussed in Section 3c, fruquintinib is taken orally, only once a day and can be taken with or without food. Regorafenib is recommended to be taken with a low-fat meal, four tablets, once a day (35). Trifluridine-tipiracil is to be taken with food, twice a day (37).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?

- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments.

As with most cancer treatments, treatment with fruquintinib is associated with side effects (see Section 3g). However, these side effects were generally well tolerated, with most treatable and manageable with supportive care and dose adjustment. In FRESCO and FRESCO-2, patients who received fruquintinib stayed on treatment for almost twice as long as those who received placebo – demonstrating the favourable efficacy and tolerability of fruquintinib compared with placebo.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

1. Background to the health economic model

The cost-effectiveness analysis for fruquintinib uses a type of health economic model known as "partitioned survival" which models costs and benefits over a patient's lifetime. This is a standard structure for economic models for cancer treatments. The model is separated into three health states; progression-free, progressed disease, and death. At the start of the model all patients are in the progression-free on treatment state, however over time patients' disease may spread and they will move to the progressed disease state or death.

Modelling impact on quantity and quality of life

The health effects captured within the analysis are a combination of quantity of life and quality of life (known in economic modelling as quality-adjusted life years [QALYs]). A QALY of 1 is equivalent to a person living for 1 year while feeling in 'perfect health'.

The percentage of modelled patients in each health state is defined by three graphs representing overall survival (how long someone might live), progression-free survival (how long the treatment will keep the disease from progressing), and time to discontinuation (TTD, how long patients are on treatment for). The trial provided follow-up for over 1 year, then the model is used to predict what could happen to a patient for the remainder of their lifetime. The clinical trials FRESCO and FRESCO-2 compared fruquintinib against BSC, so to compare against regorafenib and trifluridine-tipiracil, results from the network meta-analysis described in Section 3e were used.

Quality of life in the economic model is determined by whether a patient is in the progression-free or progressed health state, and the impact of side effects. The quality-of-life values assigned to each health state are based on the values collected in FRESCO and FRESCO-2.

Modelling costs

The health economic model looks at costs for treating and managing mCRC patients over their lifetime. This includes the costs of treatment, monitoring, supportive medications, side effects, and end-of-life care. The model used the price of fruquintinib with an NHS discount but could not factor in discounts for regorafenib and trifluridine-tipiracil as their prices are confidential.

Uncertainty

Healthcare economic modelling can be uncertain. Predicting long-term outcomes, such as treatment effectiveness or patient survival, is challenging because not all patients are followed until the end of clinical studies. Comparing different treatments is also complicated because the data often compares them to standard care, rather than directly to each other. Methods like network meta-analysis (described in 3e) help with this, but uncertainty remains. To assess the impact of these uncertainties, values for these data inputs were varied and the model calculations were-run.

2. Benefits of fruquintinib predicted by the health economic model

The economic model predicts that people with previously treated mCRC treated with fruquintinib will live longer than those treated with BSC or regorafenib or trifluridine-tipiracil. These gains mostly occur from delaying disease progression.

The trial data showed that fruquintinib was safe and well-tolerated in both the FRESCO and FRESCO-2 trials where side effects were manageable. Quality of life improvements are achieved if a patient remains progression free and alive for longer.

Based on the results of the cost-effectiveness model it is expected that in people with mCRC who have received at least two previous treatments, fruquintinib is a cost-effective treatment option, when compared with regorafenib and trifluridine-tipiracil, and BSC, from the perspective of the UK NHS. For all comparisons, the cost-effectiveness estimate (presented in a figure known as an incremental cost-effectiveness ratio [ICER]) for fruquintinib is considered cost effective when the appropriate severity modifier of 1.7 is applied (see “Additional factors”, below).

The total cost of treatment related to fruquintinib is expected to be greater than that of BSC and trifluridine-tipiracil. This is mainly because of increased costs of treatment, as patients remain on treatment with fruquintinib for longer than trifluridine-tipiracil, and BSC treatment consists mostly of cheaper concomitant medications. Compared to regorafenib, fruquintinib is predicted to be cost saving, mainly because people spend less time in the progressed disease state.

To understand how uncertainties affect things, the values for data inputs were changed. This did not change the conclusions.

3. Additional factors

NICE has introduced a special tool called a severity modifier. This modifier helps people with serious conditions get better access to effective treatments. It focuses on giving more value to QALY gains (improvement in a person's quality of life from receiving treatment) for severe diseases. Depending on how severe the condition is, the QALY gains can get a “boost” with a multiplier of either 1.2 or 1.7. The conditions that are allocated this “boost” is decided based on how many QALYs a patient might lose over their lifetime compared to someone of the same age without the condition.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Innovation Fruquintinib is a new treatment option for patients with mCRC. As described in Section 3a, it is a highly selective and potent inhibitor of three important receptors called VEGFR-1, -2, and -3, and has minimal effects on other receptors. The VEGFRs play a key role in the growth of tumours, especially in CRC. The goal in creating fruquintinib was to make an effective treatment for patients with mCRC, with a manageable safety profile. The design focuses on minimising side effects to make it easier for patients to tolerate the treatment for a longer time. Overall, clinical trials and real-world evidence indicate that fruquintinib is a promising treatment option and provides a focused and well-tolerated oral choice for patients with previously treated mCRC (41-43, 47). Of note, fruquintinib was granted an Innovation Passport as part of a scheme in the UK known as the Innovative Licensing and Access Pathway (ILAP/IP/23/16189/02; January 2024). The Innovation Passport was granted based on fruquintinib having the potential to offer benefits to a population with a significant unmet need, by providing an effective and well-tolerated oral treatment option for patients with previously treated mCRC, including those who may be more susceptible to side effects associated with currently available therapies. **QALY benefits not captured in the QALY calculation** Fruquintinib offers an alternative treatment option for patients who have received previous treatments or are not able to tolerate existing therapies. In situations where patients might only receive BSC, fruquintinib could be an alternative choice for these patients.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues relating to the use of fruquintinib have been identified.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Information relating to fruquintinib

- FRESCO (NCT02314819)
- FRESCO-2 (NCT04322539)

Information relating to colorectal cancer

- Bowel Cancer UK https://www.bowelcanceruk.org.uk/
- Cancer Research UK https://www.cancerresearchuk.org/about-cancer/bowel-cancer/living-with/resources-organisations
- MacMillan Cancer Support https://www.macmillan.org.uk/cancer-information-and-support/bowel-cancer
- National Health Service https://www.nhs.uk/conditions/bowel-cancer/help-and-support/

Further information on NICE and the role of patients

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in health technology assessments Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Active treatment: Treatment that aims to treat the disease rather than just control the symptoms

Adverse event: Side effect of a drug or other therapy – can be classified as mild, moderate, or severe

Anaemia: A low number of healthy red bloods cells, due to low levels of haemoglobin

Ascites: Collection of fluid within spaces in the abdomen

Asthenia: Physical weakness or a lack of energy

Best supportive care: Care that is not actively treating the cancer, but instead is focussed on managing symptoms and complications of disease

Biopsy: Procedure to remove a piece of tissue or a sample of cells from your body so that it can be tested in a laboratory

Clinical trial/clinical study: Research that tests how well new medical approaches work in people. They test new methods of screening, prevention, diagnosis, or treatment of a disease. They are carefully designed, reviewed, and completed, and need to be approved before they can start

Cognitive functioning: Ability to pay attention, think, understand, learn, or remember

Colonoscopy: Medical procedure in which a flexible fibre-optic instrument is inserted through the anus in order to examine the colon

Contraindication: A specific situation in which a medicine should not be used because it may be harmful to the patient

Disease control rate: How much a drug works against the disease, or keeps it from getting worse

Double-blind: Neither patients nor trial organisers know which treatment is allocated

Efficacy: Measurement of a medicine's desired effect under ideal conditions, such as a clinical trial

European Medicines Agency (EMA): Agency of the European Union in charge of the evaluation and supervision of pharmaceutical products

EORTC-QLQ C30: Cancer-specific questionnaire that measures patients' physical, psychological, and social function

EQ-5D-5L: Questionnaire used to assess five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression

Haemoglobin: The protein found in red blood cells which carries oxygen

Hand-foot syndrome: Redness, swelling, and pain on the palms of the hands and/or the soles of the feet

Hypertension: High blood pressure

Indirect treatment comparison (ITC): Statistical method used to compare treatments which are not directly compared in a trial

Leukopenia: A low number of a type of white blood cell called leukocytes

Medicines and Healthcare products Regulatory Agency (MHRA): Part of the Department of Health and Social Care in the United Kingdom which is responsible for ensuring that medicines and medical devices work and are acceptably safe

Metastasise: Primary tumour has spread to other sites in the body

Microcytic anaemia: Blood disorder where red blood cells are too small due to a lack of haemoglobin

Molecular marker: A naturally occurring molecule, gene, or other characteristic by which a particular physiological process or disease can be identified

Multicentre: A clinical trial/study that is conducted at more than one medical centre

Myelosuppression: Reduction in blood-cell production by the bone marrow. Includes anaemia, leukopenia and neutropenia

National Institute for Health and Care Excellence (NICE): Independent organisation set up by the Government to decide which drugs and treatments should be available on the NHS in England

National Health Service (NHS): Health service in the United Kingdom that provides free medical treatment for everyone and is funded by the Government

Neutropenia: A low number of a type of white blood cell called neutrophils

Neuropathy: Nerve damage that leads to pain, weakness, numbness or tingling in one or more parts of the body

Open-label: Both patients and trial organisers know which treatment is allocated

Overall survival: How long people live

Phase 3 trial/study: A clinical trial/study comparing a new treatment with the standard treatment or a placebo

Placebo: An inactive substance that looks and tastes like the medicine being tested but has no effect on the disease the new medicine is intended to treat

Placebo-controlled: Trial where there are two (or more) groups. One group receives the active treatment, the other receives the placebo. Everything else is the same between the two groups, so that any difference in their outcome can be attributed to the active treatment

Proctoscopy: Medical procedure where a doctor examines the rectum and anal cavity with a proctoscope (a hollow tube, usually with a tiny light at the end)

Progression-free survival: Time before a patient's disease worsens

Proteinuria: Presence of excess proteins in the urine

Quality-adjusted life year: Measure of disease burden that includes the length and quality of life

Quality of life: Measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living

Randomised: People allocated at random to different groups

Staging: Process to determine how much cancer is in the body (tumour size) and if it has spread

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Clarification questions

March 2024

File name	Version	Contains confidential information	Date
ID6274 Colorectal (treated) Clarification questions to PM for company-final-[Redacted].docx	1.0	No	22/03/2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Systematic literature review

A1. Appendix D, Section D.1.4 and Section D.1.5: The company submission reports that data extraction and quality assessment in the systematic literature review were conducted by one reviewer and validated by a second reviewer. Please clarify what the validation process involved.

Both data extraction (Appendix D, Section D.1.4) and quality assessment (Appendix D, Section D.1.5) of the clinical systematic literature review involved two reviewers. The first reviewer conducted the review, and a second more senior reviewer validated the review, which involved checking the accuracy of the extracted data and the quality assessment against the original publication. Disagreements were resolved through discussion or by consulting a third reviewer.

Section B: Clarification on cost-effectiveness data

Treatment effectiveness and extrapolation

B1. <u>PRIORITY.</u> Document B, Section B.3.3.2.1, P128 and Section B.3.3.2.2, P136: For both overall survival (OS) and progression free survival (PFS), the company submission states that "*The global test of the PH assumption provided a p-value less than 0.05, meaning that the null hypothesis of PH was rejected at the 95% level of confidence…*" Please provide further commentary

and justification regarding the decision to use joint models in the base case analysis given the potential for violation of the PH assumption.

In line with the recommended approach detailed in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 (1), an assessment of log-cumulative hazard and quantile-quantile plots were conducted in the model selection process, as well as the global test of the proportional hazards (PH) assumption. Although the global test of the PH assumption provided a p-value less than 0.05 for overall survival (OS) and progression-free survival (PFS), the PH assumption was assumed to hold between fruquintinib and best supportive care (BSC) based on the assessment of the respective log-cumulative hazard and quantile-quantile plots, as well as feedback from clinical and health economic experts at the United Kingdom (UK) market access advisory board (1st December 2023) (2).

As discussed in Section B.3.3.2.1 and B.3.3.2.2 for OS and PFS, respectively, assessment of the log-cumulative hazard plots (Document B, Figure 30 and Figure 37, respectively) for both endpoints suggested no violation of the PH assumption, as they were both considered parallel over time. Furthermore, the quantile-quantile plots for OS and PFS (Document B, Figure 31 and Figure 38, respectively) both produced a straight line, suggesting no violation of the accelerated failure time (AFT) assumption.

As the results of the global test of the PH assumption differed to the other two diagnostic plots, it was deemed appropriate to consult clinical and health economic experts for validation. The diagnostic plots were presented at the UK market access advisory board (1st December 2023) and health economic experts similarly concluded that, based on these tests, it was suggested that the PH assumption holds for both OS and PFS, and the assumption of a constant treatment effect was considered appropriate. For OS, it was stated that the log-cumulative hazard plot looked reasonably parallel, and the smooth hazard plot showed a similar hazard shape over time, and so it is reasonable to fit a PH model. One health economic expert stated that as the OS is short in the metastatic colorectal cancer (mCRC) population relevant to this appraisal, it was reasonable to assume PH. For PFS, experts stated that apart from the log-cumulative hazard plots crossing very early on, which was considered to be “noise” and not a cause for concern, the curves are reasonably parallel. Furthermore, clinical experts stated that there was no reason to expect there would be different hazard profiles between treatments; it was stated

that none of the treatments are expected to change the nature or trajectory of disease, but rather delay its progression. Clinical experts therefore advised that it was not appropriate to model outcomes for fruquintinib and BSC using different distributions .

In the regorafenib NICE appraisal (TA866) (3), it was agreed that the PH assumption held between all treatments, including between regorafenib and BSC, based on a similar assessment of diagnostic plots. As fruquintinib and regorafenib have similar mechanisms of action, both targeting vascular endothelial growth factor receptors (VEGFR), it is considered reasonable this assumption would also apply between fruquintinib and BSC. It should also be noted that in the trifluridine-tipiracil NICE appraisal (TA405) (4), the committee agreed that the PH assumption also held between trifluridine-tipiracil and BSC. This, in addition to the clinical expert feedback received at the UK market access advisory board (1st December 2023), further supports the use of joint models in the base case, and the application of hazard ratios (HRs) to these distributions to estimate PFS and OS for regorafenib and trifluridine-tipiracil (Question B3).

In the company submission, a scenario was presented that used the best fitting (lowest Akaike information criterion [AIC]/ Bayesian information criterion [BIC]) independent distribution for fruquintinib (log-normal for OS and PFS) and BSC (log-normal for OS and log-logistic for PFS). In both scenarios, fruquintinib remained dominant vs regorafenib, and the impact on the net health benefit [NHB] was negligible (Document B, Table 79 to Table 81).

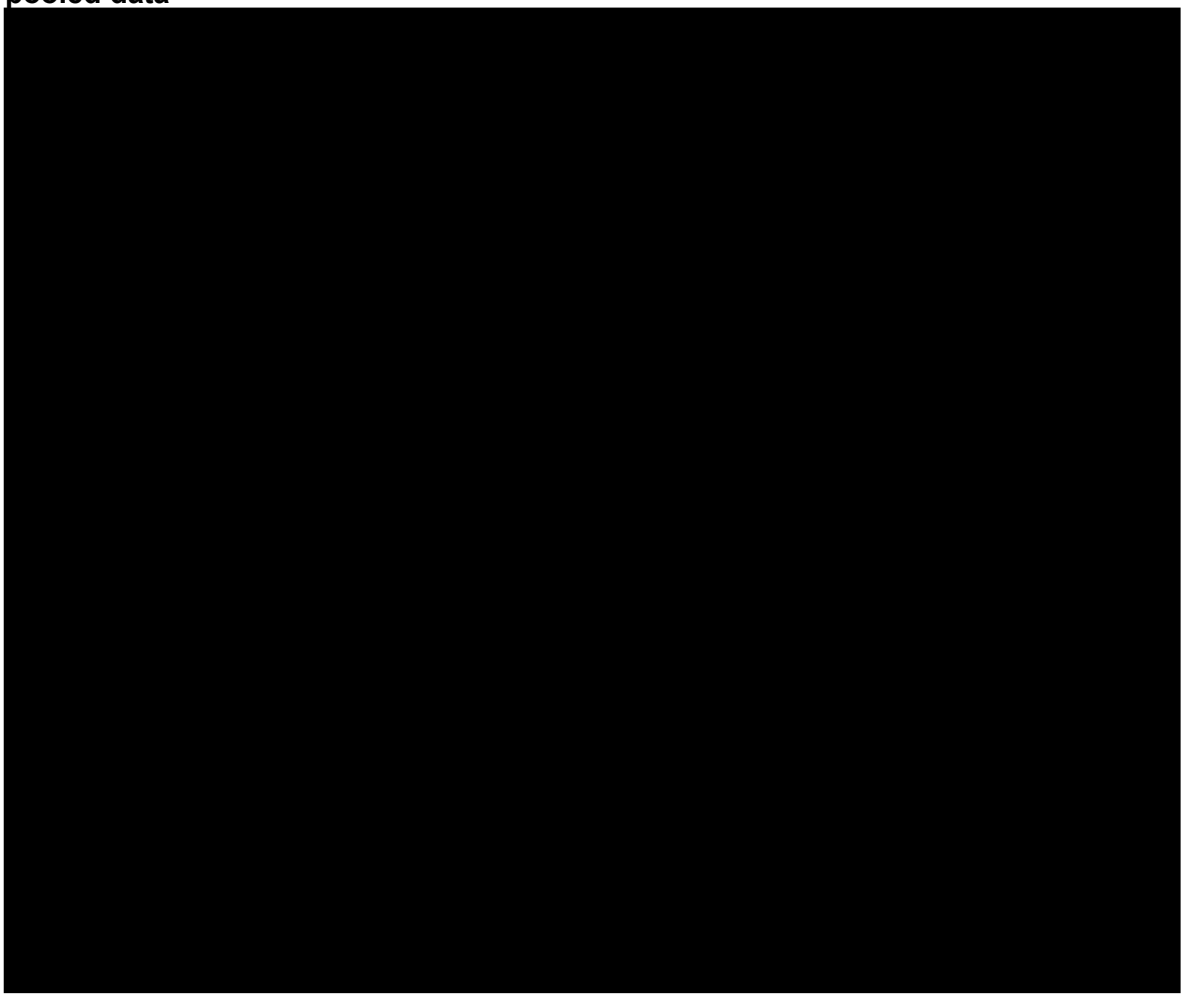
For completeness, additional scenarios using independent distributions for fruquintinib and BSC have been presented with the aim of providing reassurance that variations in model choice have minimal impact on results. The most appropriate survival curves for each endpoint were selected as per the approach detailed in Section B.3.3.2, in line with the recommended approach outlined in NICE DSU TSD 14.

Figure 1 and Figure 2 present the OS independent parametric distributions and KM curves for fruquintinib and BSC, respectively. The generalised gamma, log-normal, and log-logistic joint models were associated with the best statistical fit based on minimisation of the AIC and BIC statistics for both fruquintinib and BSC (Table 1).

Figure 1: Parametric fits for OS (independent models) compared with KM data, fruquintinib, pooled data

Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Figure 2: Parametric fits for OS (independent models) compared with KM data, BSC, pooled data



Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival.

Table 1: OS goodness-of-fit statistics for fruquintinib and BSC (independent models), pooled data

Distribution	Fruquintinib		BSC	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; OS, overall survival.

Landmark estimates of OS for each distribution and the observed data are presented in Table 2 and Table 3, for fruquintinib and BSC, respectively. Five-year survival was consistent across the distributions, and all distributions predict the median pooled FRESCO and FRESCO-2 trial survival well due to the maturity of the data. In the

fruquintinib arm, the gamma, Weibull and Gompertz distributions all predict two-year survival below 5%, which is substantially lower than the 23-month OS observed in the Kaplan-Meier (KM) data ([redacted]%). The exponential distribution overpredicts survival at one and two-years relative to the observed data in the fruquintinib arm. Therefore, these curves were not considered good visual fits to the data and were not considered in scenario analysis. Clinical expert opinion elicited during the UK market access advisory board (1st December 2023) (11) advised that for BSC, 4% of patients would be alive at two years in clinical practice, and 0% of patients would be expected to be alive at five years. The log-logistic curve predicts [redacted]% five-year survival, which was not considered clinically plausible, and was therefore not considered for scenario analysis. Clinical experts did not agree with applying different distributions by treatment arm (11), and therefore only scenarios using the same distribution for each arm were considered. The remaining distributions (generalised gamma and log-normal) are presented as scenario analyses as they provide the best statistical and visual fit to the observed fruquintinib and BSC data and provided clinically plausible long-term estimates of survival, as per clinical expert opinion.

Table 2: OS landmark estimates by parametric distribution, fruquintinib (independent models), pooled data

Distribution	1-year OS	2-year OS	5-year OS	Median (months)
Observed data (KM)	[redacted]	[redacted]	–	8.0
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Table 3: OS landmark estimates by parametric distribution, BSC (independent models), pooled data

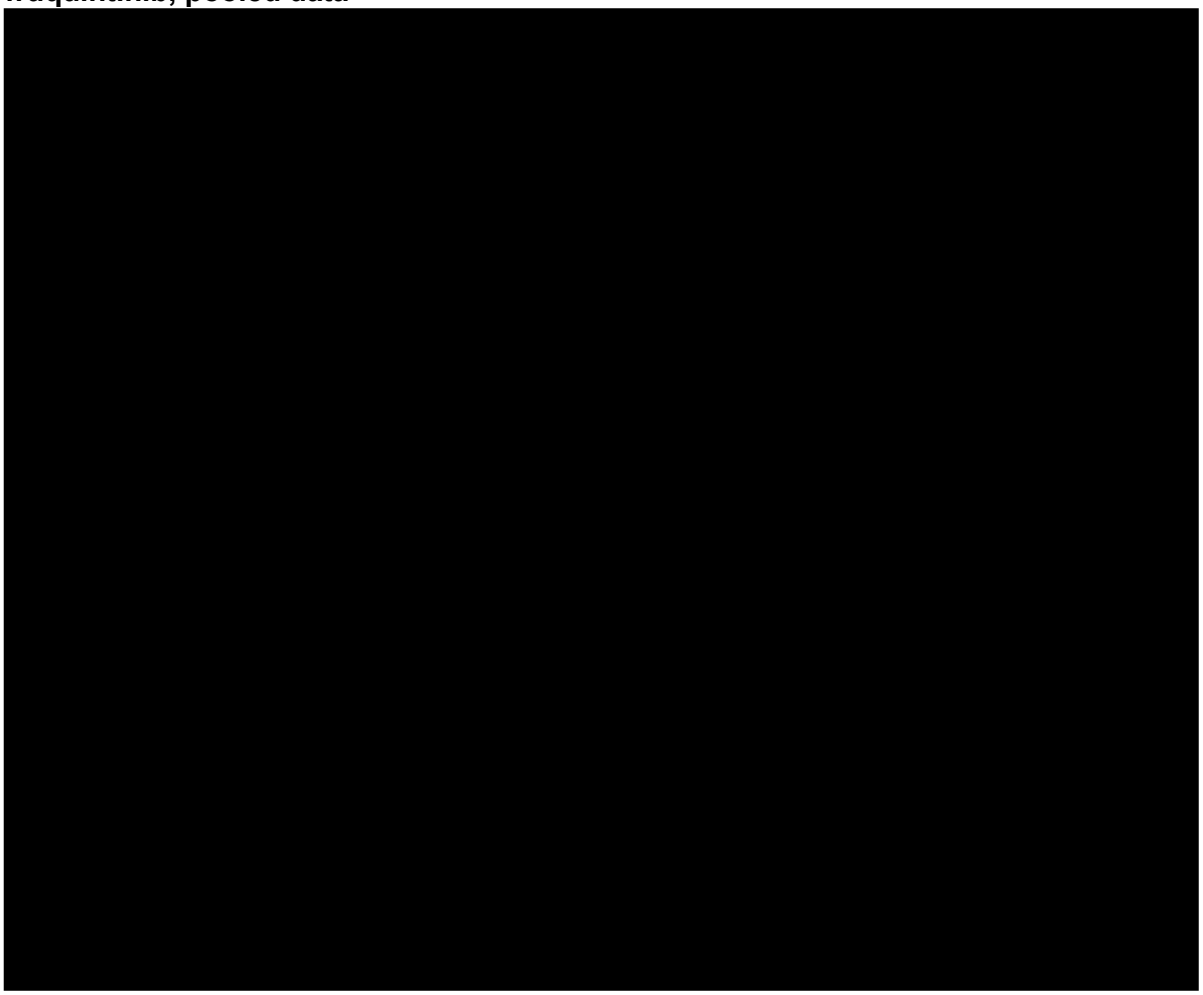
Distribution	1-year OS	2-year OS	5-year OS	Median (months)
Observed data (KM)	[redacted]	–	–	5.5
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
TA405 model result†	–	4.1%	0.6%	5.3
TA866 model result‡	18.0%	–	0.1%†	5.5†

†Using a stratified log-logistic model
‡Using a generalised gamma joint model
Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival.

Figure 3 and Figure 4 present plots of the PFS parametric distributions and KM curves for fruquintinib and BSC, respectively. The log-logistic, log-normal, and generalised gamma curves were associated with the best statistical fit based on minimisation of AIC and BIC of the seven parametric curves that were fitted (Table 4).

On visual inspection, for both fruquintinib and BSC, the exponential and Gompertz distributions do not appear to provide a good fit to the observed data, initially underpredicting PFS and then overpredicting PFS (from six months for fruquintinib and from two months for BSC) and were therefore not considered in the scenario analyses.

Figure 3: Parametric fits for PFS (independent models) compared with KM data, fruquintinib, pooled data



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Figure 4: Parametric fits for PFS (independent models) compared with KM data, BSC, pooled data

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 4: PFS goodness-of-fit statistics for fruquintinib and BSC (independent models), pooled data

Distribution	Fruquintinib		BSC	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; PFS, progression-free survival.

Landmark estimates of PFS for each distribution and the observed data are presented in Table 5 and Table 6, for fruquintinib and BSC, respectively. For fruquintinib, the Weibull and gamma distributions were considered to overpredict PFS at six months compared to the observed data, and underpredict PFS at one

year. For BSC, the gamma and Weibull distributions were considered to underpredict PFS at six months compared to the observed data. Therefore, these distributions were not considered in scenario analyses. The remaining curves predict similar one and two-year PFS for fruquintinib and BSC. Clinical expert opinion elicited during the UK market access advisory board (1st December 2023) advised that 0% of patients in either treatment arm are expected to be progression-free at two years. This is consistent with the PFS landmark estimates predicted by all distributions in the BSC arm. In the fruquintinib arm, the generalised gamma and log-logistic distributions over-predict survival compared to clinical opinion ([redacted]% and [redacted]% respectively) and were therefore not considered for scenario analysis. Based on clinical feedback at the UK market access advisory board (1st December 2023) that treatments are expected to have the same hazard profile and that it was not appropriate to model outcomes for fruquintinib and BSC using different distributions (Question B1), scenarios were only considered when the same distribution was considered appropriate for both treatment arms.

The log-normal distribution was therefore presented as a scenario analysis as it provides good statistical and visual fit to the observed fruquintinib and BSC data and provided clinically plausible long-term estimates of survival, as per clinical expert opinion.

Table 5: PFS landmark estimates by parametric distribution, fruquintinib (independent models), pooled data

Distribution	6-month PFS	1-year PFS	2-year PFS	5-year PFS	Median (months)
Observed data (KM)	[redacted]	[redacted]	–	–	3.7
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Table 6: PFS landmark estimates by parametric distribution, BSC (independent models), pooled data

Distribution	6-month PFS	1-year PFS	2-year PFS	Median (months)
Observed data (KM)	[redacted]	[redacted]	–	1.6
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
TA405 model result†	–	–	–	1.7
TA866 model result‡	–	0.2%	–	–

†Using a stratified log-logistic model.
‡Using KM followed by exponential distribution (committee preferred using the KM directly).
Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival.

Results of the scenario analyses using independent parametric curves for fruquintinib and BSC are presented in Table 7. As discussed in the Company submission (B.2.3.8.2 and B.3.11), feedback from clinical experts at the UK market access advisory board (1st December 2023) advised that trifluridine-tipiracil monotherapy is expected to be replaced in the near future by trifluridine-tipiracil in combination with bevacizumab (subject to positive NICE guidance from the ongoing appraisal ID6298), so instead the majority of fruquintinib use in UK clinical practice is expected to replace regorafenib. Therefore, the most relevant comparison for decision making was deemed to be vs regorafenib. In all scenarios, fruquintinib remains dominant compared with regorafenib. Across all comparisons, NHB estimates showed a high level of consistency with results of the base case analyses.

Table 7: Independent parametric extrapolations – scenario analysis results

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
vs regorafenib					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
Independent curves, PFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – log-normal ; PFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – gen. gamma ; PFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs trifluridine-tipiracil					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, PFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – log-normal ; PFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – gen. gamma ; PFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, PFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – log-normal ; PFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independent curves, OS – gen. gamma ; PFS – log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Incremental QALYs have been calculated assuming a 1.7x severity multiplier as requested in Question B13.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OS, overall survival; PFS, progression-free survival.

B2. Document B, Section B.3.3.2. P127-150: Please clarify whether the results of a random-effects NMA were considered for use in the economic model. If

so, please provide the results of a scenario analysis using the random-effects NMA results.

In the base case NMA, for both OS and PFS, Bayesian fixed effects (FE) models were chosen over the random effects (RE) models based on a full assessment of heterogeneity and model fit, as described in Document B, Section B.2.9.5 and Appendix D.5.1, and presented in Table 8 and Table 9.

Table 8: OS model fit assessment (random effects and fixed effects)

Model	ndata	Dbar	pD	DIC	meandev.resid	DIC.resid	tau	maxMCRatio
RE	8	-9.6960	5.172	-4.52300	7.5	12.7	0.103	0.014
FE	8	-8.5660	2.983	-5.58300	8.6	11.6	---	0.008

Note: DIC can be used to compare the fits of FE and RE models on the same data, but evaluation of network structure, abundance of information/data and clinical/methodological heterogeneity are more important factors for the choice of the heterogeneity model.
Abbreviations: DIC, deviance information criterion; FE, fixed effects; OS, overall survival; RE, random effects

Table 9: PFS model fit assessment (random effects and fixed effects)

Model	ndata	Dbar	pD	DIC	meandev. resid	DIC.resid	tau	maxMCRatio
RE	8	-9.22600	6.177	-3.04900	8.3	14.4	0.162	0.013
FE	8	-4.44100	2.983	-1.45700	13.0	16.0	---	0.008

Note: DIC can be used to compare the fits of FE and RE models on the same data, but evaluation of network structure, abundance of information/data and clinical/methodological heterogeneity are more important factors for the choice of the heterogeneity model.
Abbreviations: DIC, deviance information criterion; FE, fixed effects; PFS, progression-free survival; RE, random effects.

For both OS and PFS, the residual deviance was close to the number of data points (n=8) in each analysis. The ratio of MC error to the SD was <0.05 (0.01) in both RE and FE models, and visual inspection of density plots and trace plots suggested convergence of the models (Document B, Section B.2.9.5), thus not providing a point of differentiation between the models. However, as there are fewer than five studies per treatment comparison, the company maintain that the FE model is likely to offer more reliable results due to insufficient information to estimate between-study heterogeneity in the RE model (5). This approach is consistent with the company base case NMA in TA866 (3), although it is unclear whether the fixed or random effects model informed the committee's preferred base case. As discussed in Document B, Section B.2.9.5., visual inspection of density plots and trace plots suggested convergence of the models (see Supplementary information B2). Based on this assessment, the FE analysis is still considered the most appropriate choice of model.

For completeness, a scenario has been presented where the RE NMA is used to inform comparative efficacy in the model, demonstrating minimal impact on results.

Results of this scenario are presented in Table 10. This scenario assumes that all other inputs remain the same as the company base case, including the same parametric survival distributions for fruquintinib and BSC. Importantly, in this scenario, fruquintinib remains dominant when compared with regorafenib. The NHB vs trifluridine-tipiracil remain unchanged. The results vs BSC remain unchanged.

Table 10: RE NMA scenario analysis results

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
vs regorafenib					
Submitted base case (FE NMA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs trifluridine-tipiracil					
Submitted base case (FE NMA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC					
Submitted base case (FE NMA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RE NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Incremental QALYs have been calculated assuming a 1.7x severity multiplier as requested in Question B13.

Abbreviations: BSC, best supportive care; FE, fixed effects; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALYs, quality adjusted life years; RE, random effects; vs, versus.

B3. <u>PRIORITY.</u> Document B, Section B.3.3.2. P127-150: The EAG notes that hazard ratios from the fixed-effects NMA are used to inform survival curves for regorafenib and trifluridine-tipiracil. Please clarify whether it was also possible to obtain any overall survival (OS), progression free survival (PFS) or time to treatment discontinuation (TTD) Kaplan Meier (KM) data for regorafenib and / or trifluridine-tipiracil that could be digitalised to allow independent

survival curves to be fitted to the data. If such data are available, please provide:

- **Independently fitted survival curves (PFS, OS and TTD) to available KM data for regorafenib and trifluridine-tipiracil.**
- **A full assessment of the most appropriate survival curves in each case.**
- **An assessment of the advantages and disadvantages of fitting independent survival curves, compared to using data from the NMA.**

The base case analysis using the results of the NMA to estimate the comparative efficacy of fruquintinib with regorafenib and trifluridine-tipiracil aligns with recommendations in the NICE guide to the methods of technology appraisal, which states that "*when technologies are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate*" (6).

Importantly, the base case network meta-analysis (NMA) leverages all the available RCT evidence for fruquintinib (FRESCO (7), FRESCO-2 (8), and Xu 2017 (9)), regorafenib (CORRECT (10) and CONCUR (11)), trifluridine-tipiracil (RECOURSE (12), TERRA (13) and Yoshino 2012 (14)) and BSC (all listed trials) to estimate relative effects while preserving within-trial randomisation and is a well-established technique of synthesising data from multiple sources to estimate relative treatment effects. The use of an NMA to inform comparative efficacy also aligns with the approach accepted in TA866 (15), based on a similar evidence base. Conversely, using independent survival curves represents a naïve comparison.

For regorafenib, OS and PFS KM data are only available from the individual CORRECT (10) and CONCUR (11) trial publications. As discussed in the TA866 (3) Company submission, neither CORRECT (10) nor CONCUR (11) is considered 100% generalisable to the UK setting based on differences in prior anti-VEGF use and ethnicity between trials, and therefore using both trials (via pooling the two data sets) was considered the most robust approach for decision making; this was accepted by the NICE committee for decision making. However, the KM data for the pooled (CORRECT (10) and CONCUR (11)) is redacted in the TA866 committee papers and hence the use of the pooled KM data could not be explored in scenario

analyses. Time to discontinuation (TTD) KM data for regorafenib was not available in TA866 or the individual CORRECT and CONCUR trial publications (3, 10, 11).

For trifluridine-tipiracil, OS, PFS and TTD KM are available from a pooled dataset that includes the RECOURSE (14) and Yoshino et al (14) trials, as presented in TA405 (4). However, TERRA (13) is considered another key Phase III randomised controlled trial (RCT) assessing trifluridine-tipiracil vs BSC and was used to inform the comparative evidence base in TA866 (3). The TERRA trial data was not available for analysis at the time of Company submission in TA405 (4), but was raised as a relevant ongoing study expected to mirror the RECOURSE study. However, although OS and PFS KM are available from the TERRA trial, pooled KM data that includes all relevant trials for trifluridine-tipiracil (RECOURSE (12), TERRA (13) and Yoshino 2012 (14)) is not available and so could not be explored in scenario analyses. Similarly to regorafenib, the pooled data including all relevant trials is considered to be the most appropriate source for trifluridine-tipiracil clinical inputs given that this incorporates all of the available evidence and hence reduces uncertainty in analyses. TTD KM data was also not available for trifluridine-tipiracil in the TERRA trial (13).

Despite limitations in the data available, the OS and PFS data from the individual CORRECT and CONCUR (10, 11) trials, the OS, PFS and TTD from the pooled RECOURSE (12) and Yoshino et al (2012) (14) data reported in TA405 (12, 14), and the OS and PFS data from TERRA (13) alone were digitised and parametric distributions were fitted to these data to extrapolate over a lifetime time horizon.

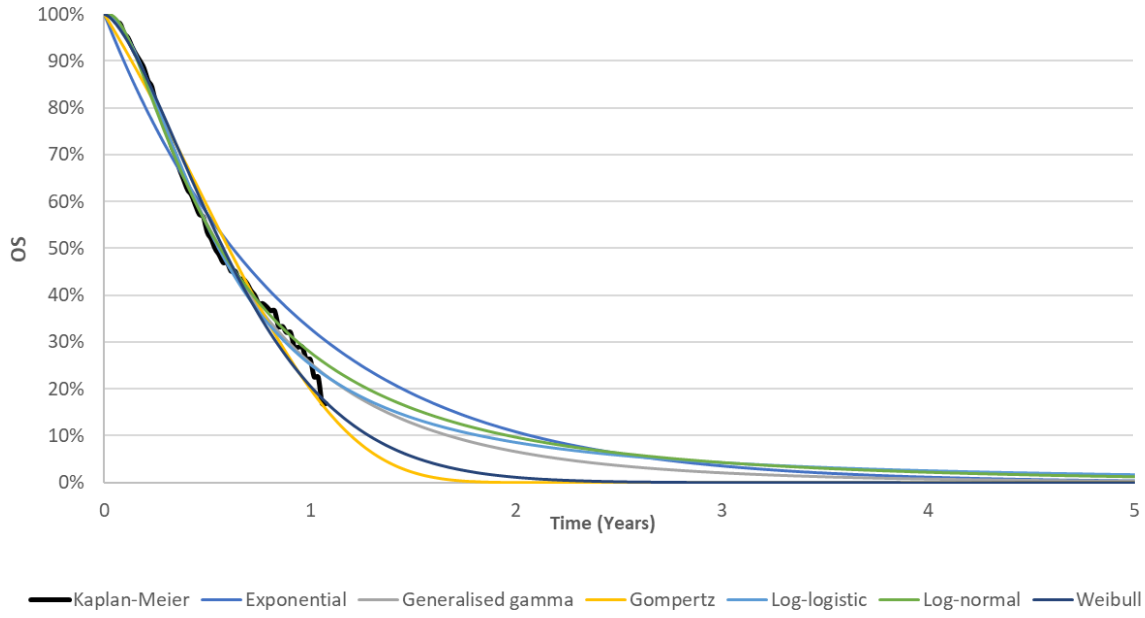
A full assessment of survival parameterisation was undertaken for the digitised KM data. Six standard parametric survival distributions were fitted to the KM data: exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma. The most appropriate parametric distribution for each endpoint was selected based on an assessment of goodness-of-fit statistics, visual fit to the observed data, and landmark estimates compared to the available published data. This aligns with the recommended approach outlined in the NICE DSU TSD 14 (1). However, at the UK market access advisory board (1st December 2023), clinical experts stated that there was no reason to expect there would be different hazard profiles between treatments (see response to question B1), therefore the base case distributions for fruquintinib and BSC (generalised gamma OS curve and log-normal PFS curve) are considered

to be the most appropriate distributions for estimating long term outcomes for regorafenib and trifluridine-tipiracil. The conclusions based on the full assessment detailed below result in the same curves being selected for regorafenib and trifluridine-tipiracil as the base case analysis, which further supports alignment.

Regorafenib (CORRECT and CONCUR) - OS

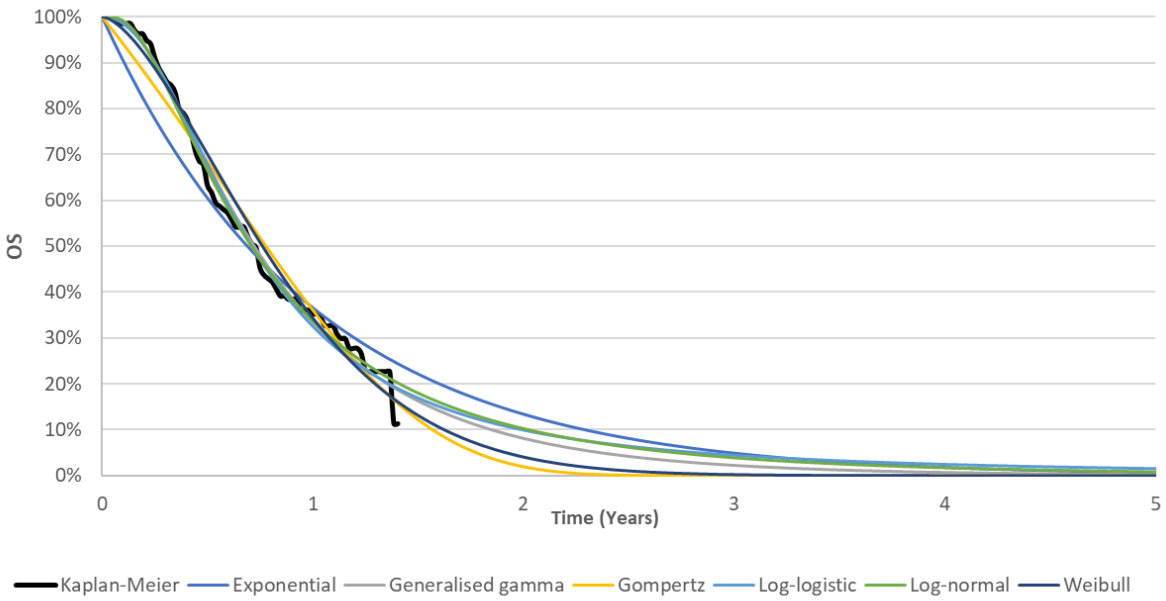
Figure 5 and Figure 6 present the regorafenib OS KM curves from CORRECT and CONCUR, respectively, alongside the parametric distributions. The log-logistic, log-normal and generalised gamma models were associated with the best statistical fit for both CORRECT and CONCUR based on minimisation of AIC and BIC statistics (Table 1). On visual inspection, for both CORRECT and CONCUR, all curves appeared to provide a good fit to the observed data in the first year, except for the exponential distribution, which initially underpredicts survival and then overpredicts survival from one year vs the observed data.

Figure 5: Parametric fits for OS compared with KM data, regorafenib (CORRECT)



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Figure 6: Parametric fits for OS compared with KM data, regorafenib (CONCUR)



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Figure 7: OS goodness-of-fit statistics for regorafenib from CORRECT and CONCUR

Distribution	CORRECT		CONCUR	
	AIC	BIC	AIC	BIC
Exponential	1,231.57	1,236.21	337.13	340.04
Weibull	1,170.24	1,179.50	314.55	320.37
Gompertz	1,202.68	1,211.95	325.29	331.11
Log-logistic	1,158.11	1,167.37	309.40	315.23
Log-normal	1,159.26	1,168.53	310.59	316.42
Generalised gamma	1,159.23	1,173.13	311.65	320.39

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival.

Landmark estimates of OS for each distribution are presented in Table 11 and Table 12 for CORRECT and CONCUR, respectively. Most of the distributions predicted similar five-year OS survival due to the maturity of the observed data in CORRECT and CONCUR. The predicted median OS values from CORRECT align with the real world evidence (RWE) studies presented in Document B (Section B.3.3.2, Table 34) (16-18).

The five-year OS estimates using the log-logistic and log-normal distributions in CORRECT and CONCUR (10, 11), overestimate survival compared to predictions from the company base case, and the model presented in TA866 (3). Using the Gompertz and Weibull distributions to extrapolate the CORRECT data results in predictions that 0% and 1.1% of patients would be alive at two years respectively

(10), which is inconsistent with advice from clinicians during the UK market access advisory board that for BSC, 4% of patients would be alive at two years in clinical practice (2). Using the Gompertz and Weibull distributions to extrapolate the CONCUR data results in predictions of two-year OS of 2.0% and 4.1% respectively, which is also implausible given the observed clinical benefit of regorafenib vs BSC in TA866 (3).

Therefore, a generalised gamma distribution was chosen to extrapolate OS for this scenario analysis as it provided a good statistical and visual fit to the observed regorafenib data in CORRECT and CONCUR and landmark estimates that align with expected survival for regorafenib (10, 11). This also aligns with the base case distributions selected for fruquintinib and BSC (Document B3, Section B.3.3.2.1).

Table 11: OS landmark estimates by parametric distribution, regorafenib (CORRECT)

Distribution	1-year OS	2-year OS	5-year OS	Median (months)
Observed data (KM)	29.5%	8.5%	–	6.2
Weibull	20.6%	1.1%	0.0%	6.9
Log-logistic	25.2%	8.6%	1.7%	6.5
Generalised gamma	25.6%	6.6%	0.3%	6.7
Log-normal	27.8%	9.7%	1.3%	6.7
Gompertz	20.0%	0.0%	0.0%	7.2
Exponential	32.9%	10.8%	0.4%	7.4
Predicted by company base-case model	[redacted]	[redacted]	[redacted]	[redacted]
TA866 model predicted value (3)	–	–	0.4%	7.1
RWE studies outlined in Document B (Section B.3.3.2, Table 34) (16-18)	–	–	–	5.6 – 7.7

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival; RWE, real world evidence; TA, technology appraisal.

Table 12: OS landmark estimates by parametric distribution, regorafenib (CONCUR)

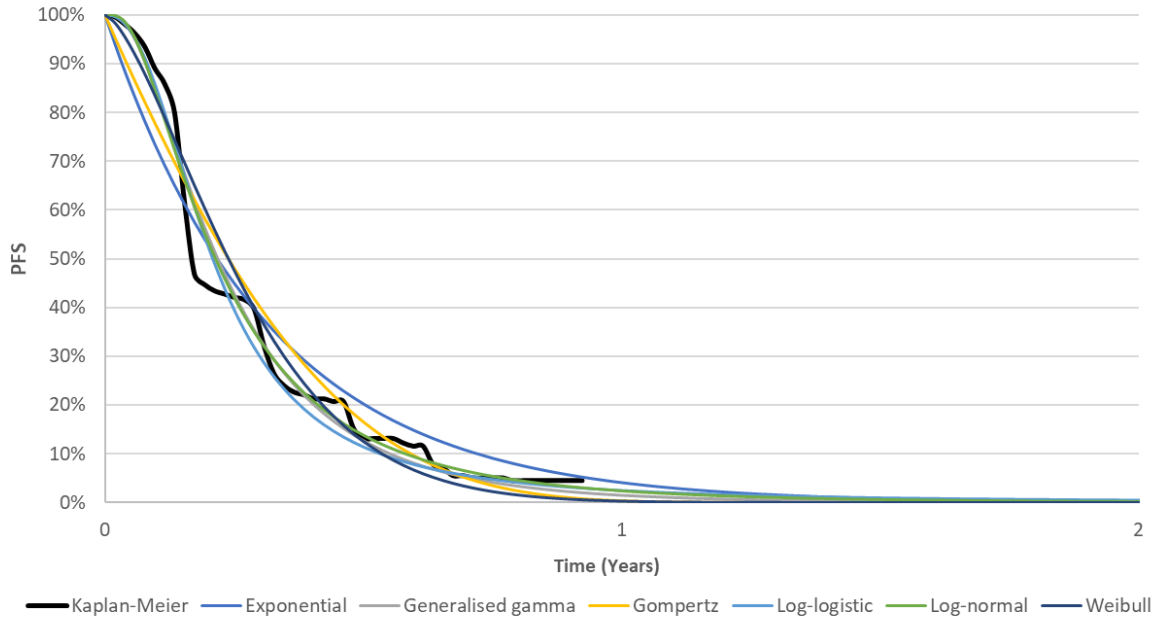
Distribution	1-year OS	2-year OS	5-year OS	Median (months)
Observed data (KM)	29.5%	8.5%	–	8.5
Weibull	34.4%	4.1%	0.0%	9.0
Log-logistic	32.6%	9.9%	1.5%	8.3
Generalised gamma	33.5%	8.1%	0.2%	8.5
Log-normal	33.7%	10.3%	0.8%	8.3
Gompertz	36.1%	2.0%	0.0%	9.2
Exponential	36.6%	13.4%	0.7%	8.1
Predicted by company base-case model	[redacted]	[redacted]	[redacted]	[redacted]
TA866 model predicted value (3)	–	–	0.4%	7.1
RWE studies outlined in Document B (Section B.3.3.2, Table 34) (16-18)	–	–	–	5.6 – 7.7

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival; RWE, real world evidence; TA, technology appraisal.

Regorafenib (CORRECT and CONCUR) - PFS

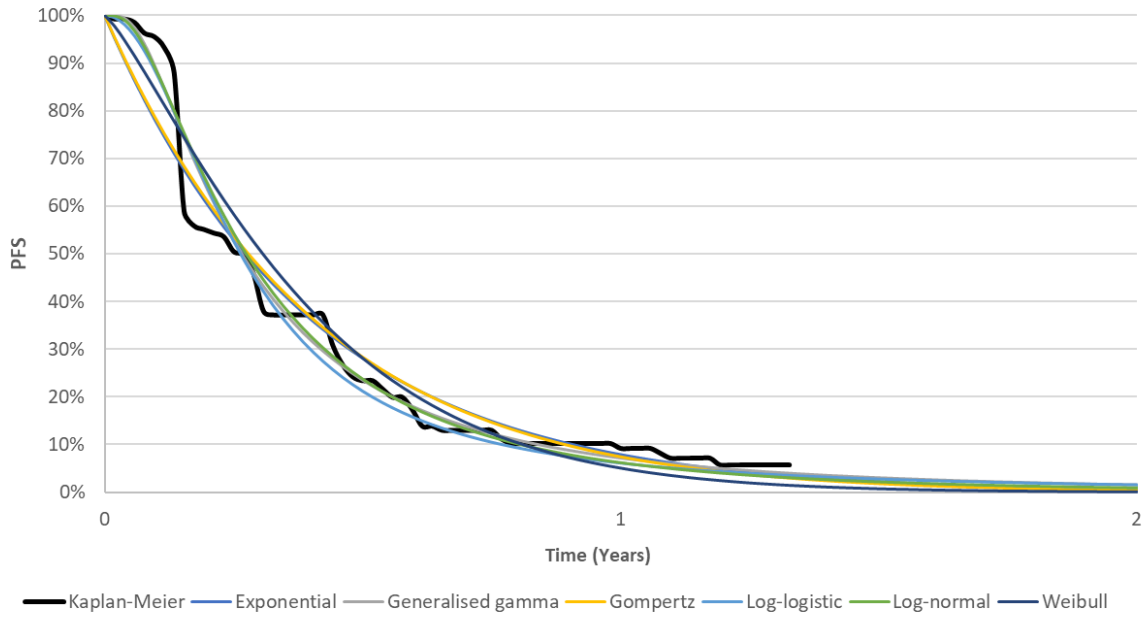
Figure 8 and Figure 9 present the CORRECT and CONCUR PFS parametric distributions and KM curves for regorafenib, respectively. PFS KM data were mature at data cut-off. The log-logistic, log-normal and generalised gamma models were associated with the best statistical fit for both CORRECT (10) and CONCUR (11) based on minimisation of AIC and BIC statistics (Table 13). On visual inspection, for the CORRECT trial, all curves appeared to provide a good fit to the observed data in the first year, except for the exponential distribution, which overpredicted survival vs the observed data. For the CONCUR trial (11), all curves appeared to provide a good visual fit to the data.

Figure 8: Parametric fits for PFS compared with KM data, regorafenib (CORRECT)



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Figure 9: Parametric fits for PFS compared with KM data, regorafenib (CONCUR)



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 13: PFS goodness-of-fit statistics for regorafenib from CORRECT and CONCUR

Distribution	CORRECT		CONCUR	
	AIC	BIC	AIC	BIC
Exponential	1,496.59	1,501.23	360.77	363.68
Weibull	1,381.38	1,390.65	354.35	360.17
Gompertz	1,463.58	1,472.85	362.64	368.46
Log-logistic	1,303.44	1,312.71	330.20	336.03
Log-normal	1,328.53	1,337.80	329.10	334.93
Generalised gamma	1,324.65	1,338.55	329.67	338.40

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Landmark estimates of PFS for each distribution are presented in Table 14 and Table 15 for CORRECT and CONCUR, respectively. Most of the distributions predicted similar two-year and five-year PFS due to the maturity of the observed data in CORRECT and CONCUR. The one-year PFS estimates based on all distributions in CONCUR, overestimate survival compared to predictions from the company base-case, and the modelled predictions presented in TA866 (3). The log-logistic and generalised gamma distributions predict that a small proportion of patients remain progression-free at five-years, which is inconsistent with clinical opinion presented in Document B (Section B.3.3.2) that 0% of patients would be progression-free at two-years. The predicted median PFS values from CORRECT (10) mostly align with the company base case predicted values, the values estimated in TA866 (3) and the RWE presented in Document B (Section B.3.3.2, Table 34) (16-18).

Therefore, a log-normal distribution was chosen for this scenario analysis as it provided a good statistical and visual fit to the observed regorafenib data in CORRECT (10) and CONCUR (11) and landmark estimates that align more closely with expected PFS for regorafenib than the other best fitting distributions. This also aligns with the base case distributions selected for fruquintinib and BSC (Document B, Section B.3.3.2.2).

Table 14: PFS landmark estimates by parametric distribution, regorafenib (CORRECT)

Distribution	6-month PFS	1-year PFS	2-year PFS	5-year PFS	Median (months)
Observed data (KM)	13.2%	-	-	-	1.8
Weibull	12.5%	0.3%	0.0%	0.0%	2.8
Log-logistic	11.4%	2.5%	0.5%	0.1%	2.3
Generalised gamma	12.7%	1.5%	0.1%	0.0%	2.5
Log-normal	13.8%	2.4%	0.2%	0.0%	2.5
Gompertz	16.5%	0.4%	0.0%	0.0%	2.8
Exponential	20.2%	4.1%	0.2%	0.0%	2.5
Predicted by company base-case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA866 model predicted value (3)	-	1.5%	-	-	2.8
RWE studies outlined in Document B (Section B.3.3.2, Table 34) (16-18)	-	7.0%	-	-	2.7-3.1

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival; RWE, real world evidence; TA, technology appraisal.

Table 15: PFS landmark estimates by parametric distribution, regorafenib (CONCUR)

Distribution	6-month PFS	1-year PFS	2-year PFS	5-year PFS	Median (months)
Observed data (KM)	23.4%	9.2%	–	–	3.0
Weibull	28.1%	5.1%	0.1%	0.0%	3.5
Log-logistic	21.2%	6.1%	1.6%	0.2%	3.0
Generalised gamma	23.5%	7.2%	1.5%	0.1%	3.0
Log-normal	23.7%	6.2%	0.9%	0.0%	3.2
Gompertz	28.3%	7.4%	0.4%	0.0%	3.2
Exponential	28.1%	7.9%	0.6%	0.0%	3.2
Predicted by company base-case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA866 model predicted value (3)	–	1.5%	–	–	2.8
RWE studies outlined in Document B (Section B.3.3.2, Table 34) (16-18)	–	7.0%	–	–	2.7-3.1

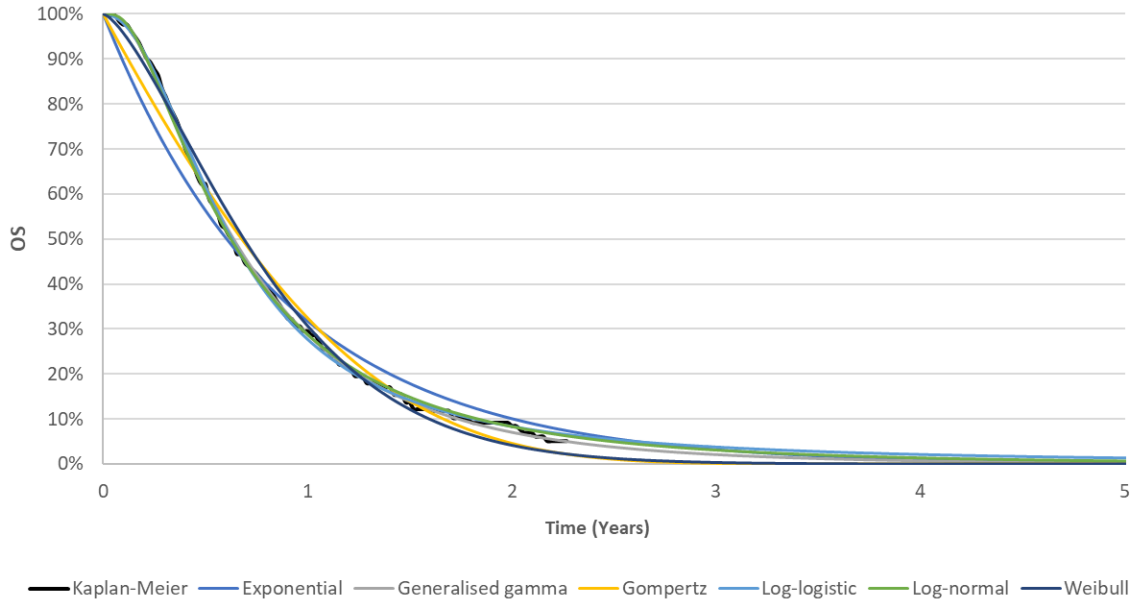
Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival; RWE, real world evidence; TA, technology appraisal.

Trifluridine-tipiracil (RECOURSE and Yoshino et al) - OS

Figure 10 presents the pooled RECOURSE (12) and Yoshino et al (2012) (14) OS parametric distributions and KM curves for trifluridine-tipiracil. OS KM data were mature at data cut-off. The log-logistic, log-normal and generalised gamma models were associated with the best statistical fit based on minimisation of the AIC and BIC

statistics (Table 16). On visual inspection, all curves appeared to provide a good fit to the observed data in the first year, except for the exponential distribution, which at first underpredicts survival compared to the observed data, and then overpredicts survival between one and two years.

Figure 10: Parametric fits for OS compared with KM data, trifluridine-tipiracil (Pooled RECOURSE and Yoshino et al)



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Table 16: OS goodness-of-fit statistics for trifluridine-tipiracil

Distribution	AIC	BIC
Exponential	1,652.61	1,657.08
Weibull	1,565.70	1,574.64
Gompertz	1,621.63	1,630.57
Log-logistic	1,530.88	1,539.82
Log-normal	1,532.97	1,541.91
Generalised gamma	1,531.73	1,545.15

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival.

Landmark estimates of OS for each distribution are presented in Table 17. Most of the distributions predicted similar five-year OS due to the maturity of the observed data. The predicted median OS values using the log-normal, log-logistic, generalised gamma, and exponential curves align most closely with the observed data, and the median values reported in the RWE (19, 20).

Therefore, a generalised gamma distribution was chosen for this scenario analysis as it provided a good statistical and visual fit to the observed trifluridine-tipiracil data

and landmark estimates that align with previously reported values. This also aligns with the base case distributions selected for fruquintinib and BSC, and regorafenib in this scenario analysis (Document B, Section B.3.3.2.1). Regorafenib and trifluridine-tipiracil were modelled jointly in TA866 (3), and therefore using the same distribution to model these treatments for this scenario analysis is suitable.

Table 17: OS landmark estimates by parametric distribution, trifluridine-tipiracil (Pooled RECOURSE and Yoshino et al)

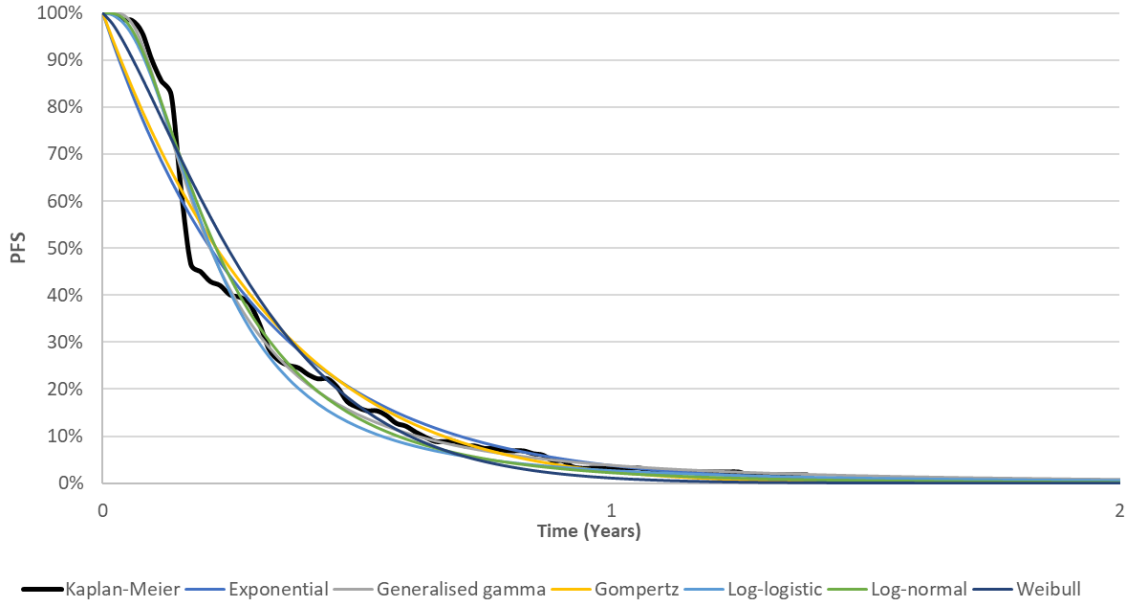
Distribution	1-year OS	2-year OS	5-year OS	Median (months)
Observed data (KM)	29.5%	8.5%	–	7.4
Weibull	30.7%	4.2%	0.0%	8.1
Log-logistic	27.7%	8.4%	1.3%	7.4
Generalised gamma	28.8%	7.1%	0.3%	7.6
Log-normal	28.8%	8.3%	0.7%	7.4
Gompertz	32.5%	4.6%	0.0%	8.1
Exponential	31.8%	10.1%	0.3%	7.2
Predicted by company base case	[redacted]	[redacted]	[redacted]	[redacted]
TA866 model predicted value (3)	–	–	1.4%	7.4
RWE studies outlined in Document B (Section B.3.3.2, Table 34) (16-18)	–	–	–	5.8 – 7.6

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival; RWE, real world evidence; TA, technology appraisal.

Trifluridine-tipiracil (RECOURSE and Yoshino et al) - PFS

Figure 11 presents the pooled RECOURSE (12) and Yoshino et al (2012) (14) PFS parametric distributions and KM curves for trifluridine-tipiracil. PFS KM data was mature at data cut-off. The log-logistic, log-normal and generalised gamma models were associated with the best statistical fit (Table 18). On visual inspection, all curves appeared to provide a good fit to the observed data after approximately four months. At the start of the observed data (first two months), the log-normal and generalised gamma distributions appear to provide a good visual fit. Between three and four months, all curves appear to overpredict survival compared to the observe data.

Figure 11: Parametric fits for PFS compared with KM data, trifluridine-tipiracil (pooled RECOURSE and Yoshino et al)



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 18: PFS goodness-of-fit statistics for trifluridine-tipiracil

Distribution	AIC	BIC
Exponential	1,639.54	1,644.02
Weibull	1,566.49	1,575.43
Gompertz	1,635.47	1,644.41
Log-logistic	1,425.85	1,434.79
Log-normal	1,419.95	1,428.90
Generalised gamma	1,400.40	1,413.81

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Landmark estimates of PFS for each distribution are presented in Table 19. Most of the distributions predicted similar two-year and five-year PFS due to the maturity of the observed data. The one-year PFS estimates using all distributions overestimated survival compared to predictions from the company base case. The log-logistic and generalised gamma distributions predict that a small proportion of patients remain progression-free at five-years, which is inconsistent with clinical opinion presented in Document B (Section B.3.3.2) that 0% of patients would be progression-free at two-years. The predicted median PFS values using the generalised gamma distribution are not well aligned with the estimated survival in TA866 (3), and the estimates RWE presented in Document B (Section B.3.3.2, Table 34) (16-18).

Therefore, a log-normal distribution was chosen for this scenario analysis as it provided a good statistical and visual fit to the observed trifluridine-tipiracil data. This also aligns with the base-case distributions selected for fruquintinib and BSC, and regorafenib in this scenario analysis (Document B, Section B.3.2.2.2). Regorafenib and trifluridine-tipiracil were modelled jointly in TA866 (3), and therefore using the same distribution to model these treatments for this scenario analysis is appropriate. Given that the PH assumption is assumed to hold for all treatments vs BSC (see response to clarification question B1), it is also appropriate for the selected distributions to align with those chosen for fruquintinib and BSC. This approach aligns with clinical expert feedback received at the UK market access advisory board (2) (clarification question B1).

Table 19: PFS landmark estimates by parametric distribution, trifluridine-tipiracil

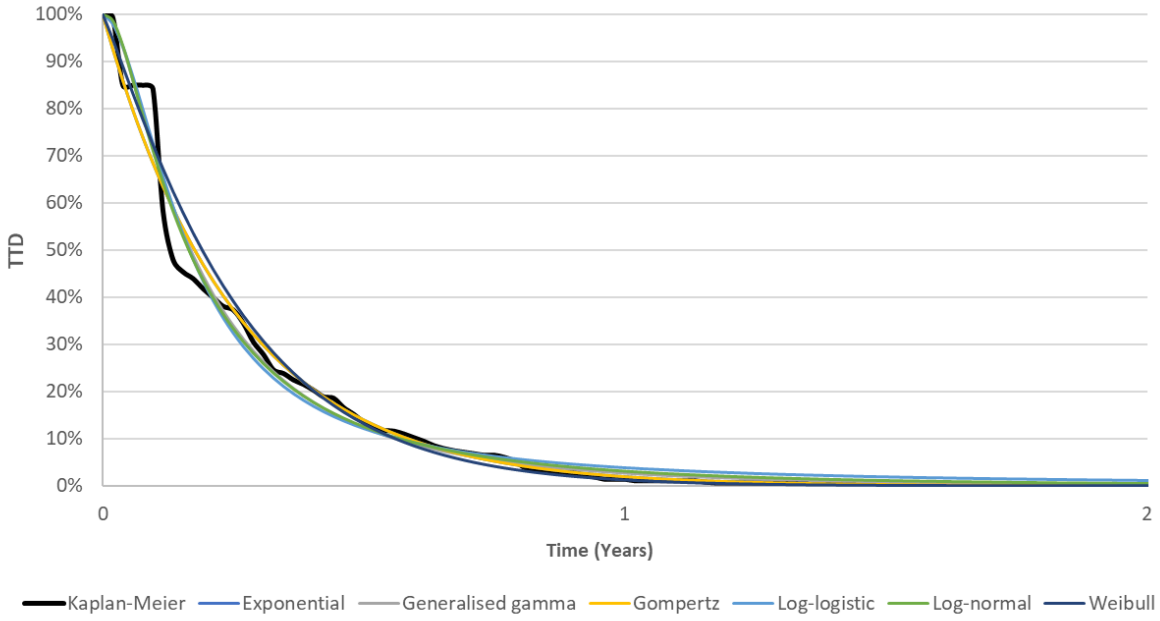
Distribution	6-month PFS	1-year PFS	2-year PFS	5-year PFS	Median (months)
Observed data (KM)	16.2%	3.2%	-	-	1.8
Weibull	16.7%	1.1%	0.0%	0.0%	2.8
Log-logistic	12.1%	2.7%	0.6%	0.1%	2.5
Generalised gamma	14.7%	3.8%	0.8%	0.1%	2.3
Log-normal	14.0%	2.2%	0.2%	0.0%	2.5
Gompertz	19.2%	2.4%	0.0%	0.0%	2.5
Exponential	19.4%	3.8%	0.1%	0.0%	2.3
Predicted by company base-case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA866 model predicted value (3)	-	-	-	-	2.9
RWE studies outlined in Document B (Section B.3.3.2, Table 34) (16-18)	-	-	-	-	3.2 – 3.3

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival; RWE, real world evidence; TA, technology appraisal.

Trifluridine-tipiracil (RECOURSE and Yoshino et al) - TTD

Figure 12 presents the pooled RECOURSE (12) and Yoshino et al (2012) (14) TTD parametric distributions and KM curves for trifluridine-tipiracil. All curves provided a good visual fit to the data. A log-normal distribution was chosen to model trifluridine-tipiracil TTD for this scenario analysis as it provided the best statistical fit (Table 20), and a good visual fit to the observed trifluridine-tipiracil data. The log-normal distribution also aligns with the distribution choice for trifluridine-tipiracil PFS, and the base case fruquintinib TTD curve.

Figure 12: Parametric fits for TTD compared with KM data, trifluridine-tipiracil



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 20: TTD goodness-of-fit statistics for trifluridine-tipiracil

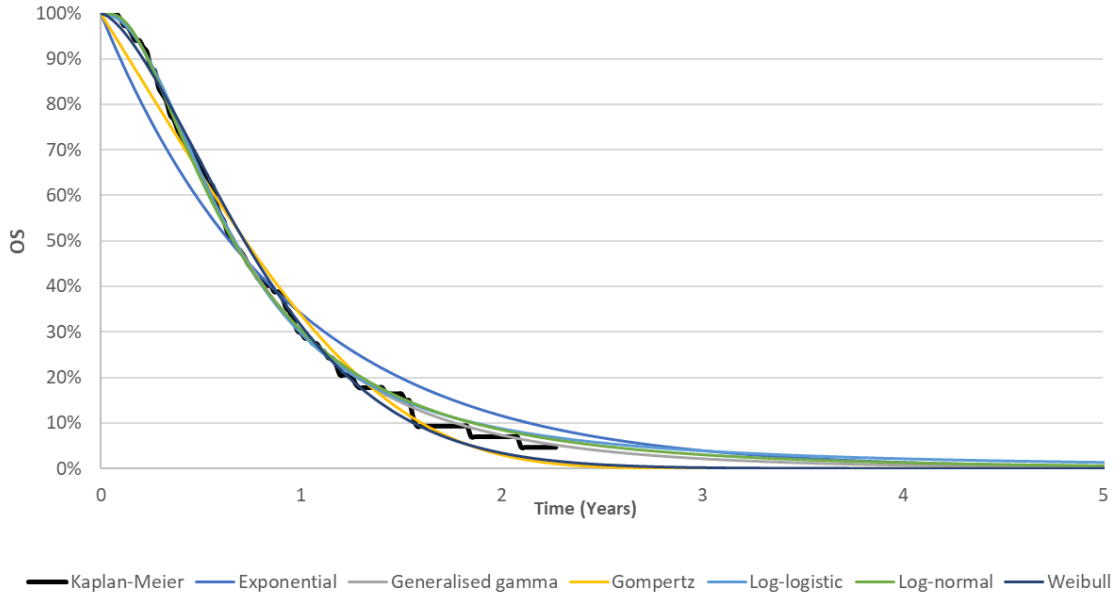
Distribution	AIC	BIC
Exponential	1,861.00	1,865.47
Weibull	1,850.63	1,859.57
Gompertz	1,863.00	1,871.94
Log-logistic	1,813.30	1,922.25
Log-normal	1,794.20	1,803.14
Generalised gamma	1,794.67	1,808.09

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Trifluridine-tipiracil (TERRA) - OS

Figure 13 presents the OS parametric distributions and KM curves for trifluridine-tipiracil from TERRA (13). OS KM data were mature at data cut-off. The log-logistic, log-normal and generalised gamma models were associated with the best statistical fit based on minimisation of the AIC and BIC statistics (Table 21). On visual inspection, all curves appeared to provide a good fit to the observed data other than the exponential distribution, which appears to underpredict survival in the first year compared to the observed data, and then overpredict survival after one-year.

Figure 13: Parametric fits for OS compared with KM data, trifluridine-tipiracil (TERRA)



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Table 21: OS goodness-of-fit statistics for trifluridine-tipiracil (TERRA)

Distribution	AIC	BIC
Exponential	664.46	668.06
Weibull	618.87	626.08
Gompertz	644.10	651.31
Log-logistic	609.73	616.93
Log-normal	607.09	614.30
Generalised gamma	608.50	619.31

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, Overall survival.

Landmark estimates of OS for each distribution are presented in Table 22. Most of the distributions predicted similar five-year OS due to the maturity of the observed data. The predicted median OS values using the log-normal, log-logistic and generalised gamma align most closely with the observed data, and the median values reported in the RWE (19, 20).

Therefore, a generalised gamma distribution was chosen for this scenario analysis as it provided a good statistical and visual fit to the observed trifluridine-tipiracil data and landmark estimates that align with previously reported values. This also aligns with the base case distributions selected for fruquintinib and BSC, and regorafenib in this scenario analysis (Document B, Section B.3.3.2.1).

Table 22: OS landmark estimates by parametric distribution, trifluridine-tipiracil (TERRA)

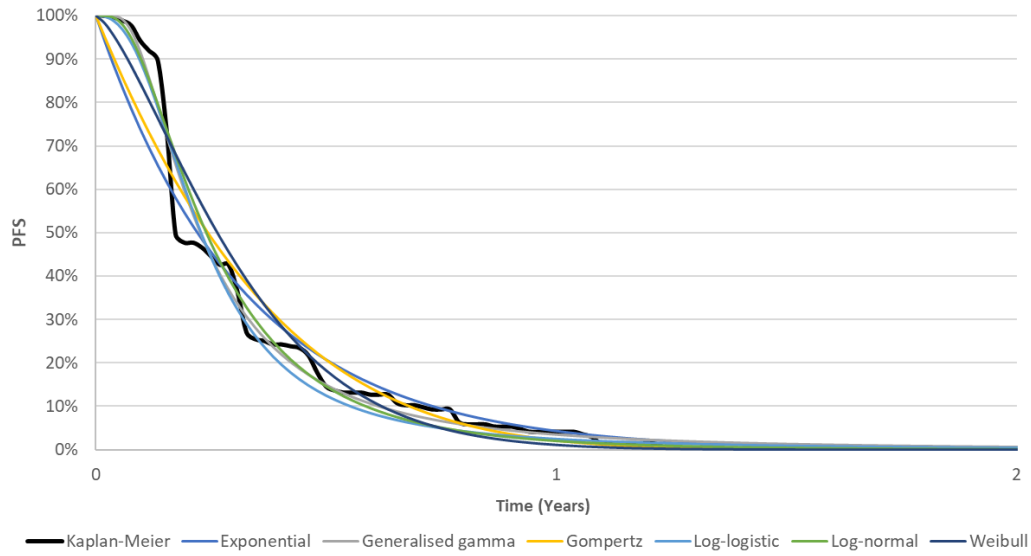
Distribution	1-year OS	2-year OS	5-year OS	Median (months)
Observed data (KM)	29.7%	7.0%	–	7.8
Weibull	31.4%	3.4%	0.0%	8.5
Log-logistic	29.6%	8.8%	1.3%	7.8
Generalised gamma	30.2%	7.3%	0.3%	7.8
Log-normal	30.4%	8.5%	0.6%	7.8
Gompertz	33.7%	3.0%	0.0%	8.5
Exponential	34.0%	11.6%	0.5%	7.6
Predicted by company base case	[redacted]	[redacted]	[redacted]	[redacted]
TA866 model predicted value (3)	–	–	1.4%	7.4
RWE studies outlined in Document B (Section B.3.3.2, Table 34) (16-18)	–	–	–	5.8–7.6

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival; RWE, real world evidence; TA, technology appraisal.

Trifluridine-tipiracil (TERRA) - PFS

Figure 11 presents the PFS parametric distributions and KM curves for trifluridine-tipiracil from the TERRA trial (13). PFS KM data was mature at data cut-off. The log-logistic, log-normal and generalised gamma models were associated with the best statistical fit (Table 23). On visual inspection, all curves appeared to provide a good fit to the observed data after around six months. At the start of the observed data, none of the curves appear to provide a consistently good fit.

Figure 14: Parametric fits for PFS compared with KM data, trifluridine-tipiracil (TERRA)



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 23: PFS goodness-of-fit statistics for trifluridine-tipiracil (TERRA)

Distribution	AIC	BIC
Exponential	658.95	662.55
Weibull	617.21	624.41
Gompertz	653.02	660.23
Log-logistic	556.99	564.19
Log-normal	552.84	560.04
Generalised gamma	544.17	554.98

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Landmark estimates of PFS for each distribution are presented in Table 24. Most of the distributions predicted similar two-year and five-year PFS due to the maturity of the observed data. The generalised gamma distribution predicts that a small proportion of patients remain progression-free at five-years, which is inconsistent with clinical opinion presented in Document B (Section B.3.3.2) that 0% of patients would be progression-free at two-years. The predicted median PFS values using the generalised gamma and log-logistic distributions are not well aligned with the values estimated in TA866 (3), and the RWE presented in Document B (Section B.3.3.2, Table 34) (16-18).

Therefore, a log-normal distribution was chosen for this scenario analysis as it provided a good statistical and visual fit to the observed trifluridine-tipiracil data. This also aligns with the base-case distributions selected for fruquintinib and BSC, and regorafenib in this scenario analysis (Document B, Section B.3.2.2.2), and the distribution selected for trifluridine-tipiracil using the pooled RECOURSE (12) and Yoshino et al (2012) (14) data.

Table 24: PFS landmark estimates by parametric distribution, trifluridine-tipiracil (TERRA)

Distribution	6-month PFS	1-year PFS	2-year PFS	5-year PFS	Median (months)
Observed data (KM)	14.6%	4.1%	–	–	1.8
Weibull	18.3%	1.1%	0.0%	0.0%	3.0
Log-logistic	12.5%	2.5%	0.5%	0.0%	2.5
Generalised gamma	14.9%	3.5%	0.6%	0.1%	2.5
Log-normal	14.6%	2.0%	0.1%	0.0%	2.8
Gompertz	20.7%	2.1%	0.0%	0.0%	2.8
Exponential	20.8%	4.3%	0.2%	0.0%	2.5
Predicted by company base-case model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA866 model predicted value (3)	–	–	–	–	2.9
RWE studies outlined in Document B (Section B.3.3.2, Table 34) (16-18)	–	–	–	–	3.2–3.3

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival; RWE, real world evidence; TA, technology appraisal.

For completeness, Table 25 presents results of a scenario analysis using digitised data to predict PFS and OS for regorafenib, and to predict PFS, OS and TTD for trifluridine-tipiracil. The approach used to model TTD for regorafenib in all scenarios and trifluridine-tipiracil in the TERRA (13) scenario is aligned with that of the base-case (Document B, Section 3.3.2.3). However, the company maintains that the use of an NMA to inform comparative efficacy is the most robust approach in line with recommendations in the NICE guide to the methods of technology appraisal (6).

Fruquintinib remains dominant when compared with regorafenib in all scenarios. The NHB vs trifluridine-tipiracil is increased from [redacted] to [redacted] when using the pooled RECOURSE (12) and Yoshino et al (2012) (14) data. The NHB vs trifluridine-tipiracil is increased from [redacted] to [redacted] when using the TERRA trial data (13). The results vs BSC remain unchanged. In all presented scenario analysis, the severity modifier remains 1.7 vs all comparators.

Table 25: Digitised data scenario analysis results

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
vs regorafenib					

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and Regorafenib (CORRECT) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and Regorafenib (CONCUR) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (TERRA) and Regorafenib (CORRECT) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (TERRA) and Regorafenib (CONCUR) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs trifluridine-tipiracil					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and Regorafenib (CORRECT) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and Regorafenib (CONCUR) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (TERRA) and Regorafenib (CORRECT) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
Digitised trifluridine-tipiracil (TERRA) and Regorafenib (CONCUR) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and Regorafenib (CORRECT) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and Regorafenib (CONCUR) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (TERRA) and Regorafenib (CORRECT) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Digitised trifluridine-tipiracil (TERRA) and Regorafenib (CONCUR) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Incremental QALYs have been calculated assuming a 1.7x severity multiplier as requested in Question B13.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OS, overall survival; PFS, progression-free survival; RE, random effects.

B4. Document B, Section B.3.3.2. P127-150: Please provide further justification on the decision to pool the FRESCO and FRESCO-2 studies for parameterising the economic model. Please comment on which study more closely reflects UK clinical practice. Please also comment on whether using that study to

parameterise OS, PFS and TTD would be likely to lead to a substantial impact on the ICER.

As discussed in Section B.2.6.3.1, the pooled FRESCO and FRESCO-2 data (21) were considered the best use of the available evidence base to inform the economic model based on clinician feedback from both the UK oncologist advisory board (22nd September 2023) (22) and the UK market access advisory board (1st December 2023) (21). The pooled data utilises both large RCTs in the population of interest, provides a greater sample size (total number of patients = 1,107) to inform the analysis and reduces uncertainty in clinical inputs in the economic model, and importantly, reflects a population that is more representative of the UK landscape vs using either FRESCO (7) or FRESCO-2 (8) independently. The approach of using pooled trial datasets as the source of clinical inputs for the economic model also aligns with the committee-preferred approach in both the regorafenib and trifluridine-tipiracil appraisals, where the evidence base of each individual trial was also considered to be less representative of UK clinical practice compared to the pooled data (TA866 (3) and TA405 (4)).

Neither FRESCO (7) nor FRESCO-2 (8) can be considered more reflective of UK practice vs the other. Advisors at the UK oncologist advisory board (22nd September 2023) (22) stated that FRESCO (7) is considered more representative of the UK population's current low rate of prior exposure to anti-VEGF treatments (e.g. bevacizumab), while FRESCO-2 (8) is considered more representative of the UK population with respect to age and ethnicity. Therefore, the two trials pooled together provide a population that is more representative of the UK landscape than if either FRESCO (7) or FRESCO-2 (8) were used independently (21, 23, 24). Advisors further stated that both FRESCO (7) and FRESCO-2 (8) offer strong and compelling data packages that complement each other well, that both trials are highly relevant for clinical decision-making for the population of interest, and that together they comprise an evidence base generalisable to the UK patient population (2).

It is therefore not considered appropriate to inform the economic model using either FRESCO (7) or FRESCO-2 (8) data alone. However, for completeness, scenario analyses are presented using data from FRESCO (7) and FRESCO-2 (8) individually to inform clinical inputs for fruquintinib and BSC.

An assessment of survival parameterisation was undertaken for the FRESCO (7) and FRESCO-2 (8) data using the approach taken in clarification question B1 and clarification question B3. A joint generalised gamma parametric model was selected for OS and a joint log-normal parametric model was selected for PFS and TTD. The PH assumption is assumed to hold for the individual trials, given the clinical expert feedback as outlined in clarification question B1 and in line with reasoning from TA866 (3). The selected models provided a good statistical fit to the data (see model), ranking amongst the lowest with respect to AIC/BIC statistics in all cases. Figure 15 presents the OS KM data for FRESCO (7) and FRESCO-2 (8) independently in comparison to the pooled KM data. Figure 16 presents the chosen parametric OS curves for this scenario analysis for the individual FRESCO (7) and FRESCO-2 (8) trials. Figure 17 and Figure 18 present the KM curves and chosen distributions for PFS respectively, whilst Figure 19 presents the fruquintinib TTD data from FRESCO (7) and FRESCO-2 (8), respectively. The chosen distributions provide a good visual fit to the observed data.

Figure 15: OS KM data, (pooled data, FRESCO and FRESCO-2)

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival.

Figure 16: OS parametric fits to the KM data (FRESCO and FRESCO-2)

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival.

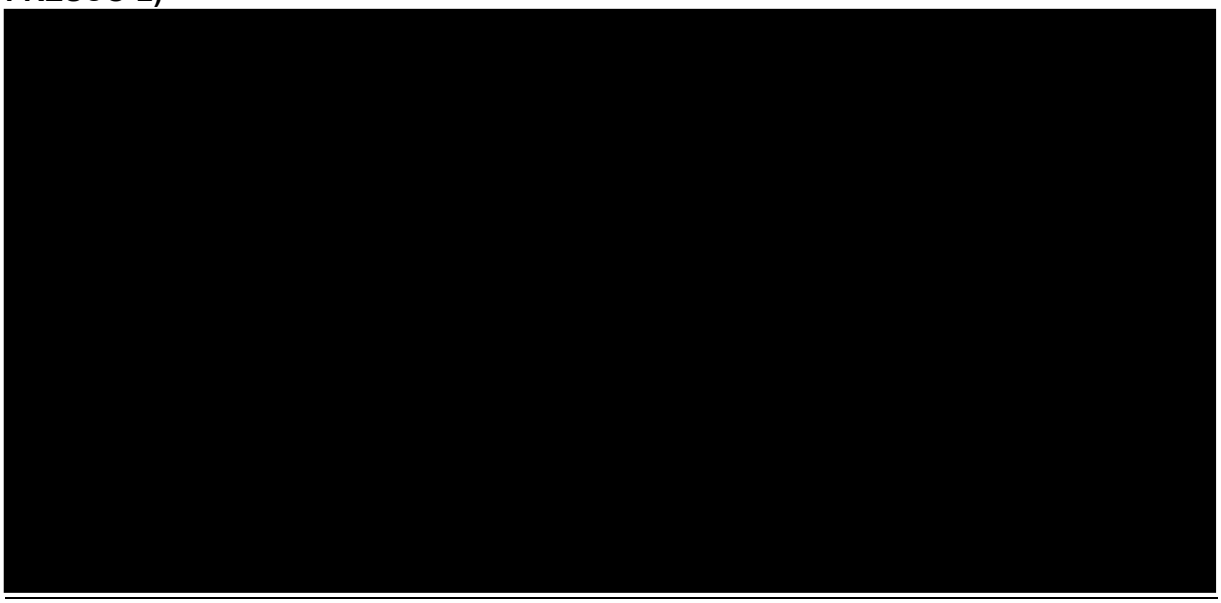
Figure 17: PFS KM data (pooled data, FRESCO and FRESCO-2)

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival.

Figure 18: PFS parametric fits to the KM data (FRESCO and FRESCO-2)

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival.

Figure 19: TTD parametric fits compared with KM data (pooled data, FRESCO and FRESCO-2)



Abbreviations: KM, Kaplan-Meier; TTD, time-to-treatment discontinuation.

Other model inputs that were informed using the pooled FRESCO and FRESCO-2 data (21) have been updated to the respective individual trial source for this analysis (FRESCO (7) and FRESCO-2 (8)). Baseline characteristics, Grade ≥3 treatment-related TEAEs and Grade 1-2 treatment-related TEAEs, concomitant medications, RDI, and subsequent therapy proportions by trial are presented in Table 29 to Table 40. Other inputs in the model are aligned with the base case analysis. Health-related

quality of life (HRQoL) was measured in FRESCO-2 (8) only (Document B, Section B.3.5.1) and as a result, utility inputs remain consistent across this scenario analysis.

Table 26: Baseline characteristics; FRESCO and FRESCO-2

Variable	Value (FRESCO)	Value (FRESCO-2)
Baseline age, years	54.6	62.2
Male, %	61.3	55.7
Body weight, kg	64.40	73.69
BSA, m^2	1.72	1.85

Abbreviations: RDI, relative dose intensity.

Table 27: Grade ≥3 treatment-related TEAEs reported in ≥2% of patients in any treatment arm, as applied in the model

Adverse event	FRESCO		FRESCO-2	
	Fruquintinib N=278 n (%)	BSC N=137 n (%)	Fruquintinib N=456 n (%)	BSC N=230 n (%)
Anaemia	0 (0)	0 (0)	1 (0.2)	4 (1.7)
Asthenia	0 (0)	0 (0)	24 (5.3)	3 (1.3)
Diarrhoea	8 (2.9)	0 (0)	15 (3.3)	0 (0)
Fatigue	3 (1.1)	0 (0)	15 (3.3)	1 (0.4)
Hand-foot syndrome	30 (10.8)	0 (0)	28 (6.1)	0 (0)
Hypertension	59 (21.2)	3 (2.2)	49 (10.7)	2 (0.9)
Aspartate aminotransferase increased	1 (0.4)	1 (0.7)	2 (0.4)	1 (0.4)
Hyperbilirubinaemia	4 (1.4)	2 (1.5)	0 (0)	0 (0)
Leukopenia	1 (0.4)	0 (0)	0 (0)	0 (0)
Neutropenia	0 (0)	0 (0)	0 (0)	1 (0.4)
Rash	0 (0)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	7 (2.5)	0 (0)	0 (0)	1 (0.4)
Lymphopenia	0 (0)	0 (0)	0 (0)	0 (0)
Proteinuria	9 (3.2)	0 (0)	7 (1.5)	1 (0.4)
Anorexia	0 (0)	0 (0)	0 (0)	0 (0)
Decreased appetite	3 (1.1)	0 (0)	6 (1.3)	2 (0.9)
Febrile neutropenia	0 (0)	0 (0)	0 (0)	0 (0)
Mucositis	0 (0)	0 (0)	0 (0)	0 (0)
Hypophosphataemia	0 (0)	0 (0)	0 (0)	0 (0)
Lipase level increased	0 (0)	0 (0)	1 (0.2)	0 (0)
Platelet count decreased	7 (2.5)	0 (0)	0 (0)	0 (0)

†Where AE data were not reported the value was assumed to be zero.
Abbreviations: BSC, best supportive care; TEAE, treatment-emergent adverse event.

Table 28: Grade 1-2 treatment-related TEAEs reported in ≥10% of patients in any treatment arm, as applied in the model

Adverse event	FRESCO		FRESCO-2	
	Fruquintinib N=278 n (%)	BSC N=137 n (%)	Fruquintinib N=456 n (%)	BSC N=230 n (%)
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Anorexia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Fever	[redacted]	[redacted]	[redacted]	[redacted]
Hand-foot skin reaction	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Oral Mucositis	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Weight loss	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Voice changes	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Increased alanine aminotransferase	[redacted]	[redacted]	[redacted]	[redacted]
Increased total bilirubin	[redacted]	[redacted]	[redacted]	[redacted]
Hyperbilirubinaemia	[redacted]	[redacted]	[redacted]	[redacted]
Increase in alkaline phosphatase	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood thyroid stimulating hormone increased	[redacted]	[redacted]	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decrease	[redacted]	[redacted]	[redacted]	[redacted]
Occult blood positive	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]

†Where AE data were not reported the value was assumed to be zero.
Abbreviations: BSC, best supportive care; TEAE, treatment-emergent adverse events.

Table 29: Concomitant medications; FRESCO and FRESCO-2

Variable	FRESCO		FRESCO-2	
	Fruquintinib N=278 n (%)	BSC N=138 n (%)	Fruquintinib N=461 n (%)	BSC N=230 n (%)
Analgesics	237 (45.7)	56 (40.6)	336 (72.9)	162 (70.4)
Anti-inflammatory and anti-rheumatic products	91 (32.7)	23 (16.7)	130 (28.2)	77 (33.5)
Psycholeptics	56 (20.1)	10 (7.2)	141 (30.6)	60 (26.1)
Drugs for constipation	39 (14.0)	24 (17.4)	124 (26.9)	76 (33.0)
Corticosteroids for systemic use	43 (15.5)	29 (21.0)	135 (29.3)	53 (23.0)
Anti-emetics and anti-nauseants	29 (10.4)	15 (10.9)	121 (26.2)	53 (23.0)
Diuretics	40 (14.4)	16 (11.6)	104 (22.6)	49 (21.3)
Blood substitutes and perfusion solutions	72 (25.9)	25 (18.1)	71 (15.4)	28 (12.2)
Drugs for functional gastrointestinal disorders	47 (16.9)	15 (10.9)	73 (15.8)	34 (14.8)
Mineral supplements	25 (9.0)	15 (10.9)	91 (19.7)	33 (14.3)
Vitamins	25 (9.0)	6 (4.3)	76 (16.5)	34 (14.8)
Anti-anaemic preparations	37 (13.3)	7 (5.1)	21 (4.6)	21 (9.1)
Psychoanaleptics	4 (1.4)	8 (5.8)	47 (10.2)	9 (3.9)

Abbreviations: RDI, relative dose intensity.

Table 30: Relative dose intensity

Treatment	RDI
FRESCO	92.0%
FRESCO-2	85.0%

Abbreviations: RDI, relative dose intensity.

Table 31: Subsequent therapies used in the model, FRESCO and FRESCO-2 data

Subsequent therapy	FRESCO				FRESCO-2			
	Fruquintinib, %	BSC %	Regorafenib, %	Trifluridine-tipiracil, %	Fruquintinib, %	BSC, %	Regorafenib, %	Trifluridine-tipiracil, %
At least 1 subsequent therapy	42.4	50.7	42.4	42.4	29.4	34.3	29.4	29.4
Fluorouracil	61.2	64.2	61.2	61.2	16.4	18.3	19.6	17.2
Regorafenib	0	0	0	0	16.0	15.0	0	16.7
Oxaliplatin	0	0	0	0	13.6	12.5	16.2	14.3
Bevacizumab	20.4	23.2	20.4	20.4	9.9	12.5	11.7	10.3
Folinic acid	0	0	0	0	8.5	10.0	10.0	8.9
Capecitabine	0	0	0	0	11.7	8.3	14.0	12.3
Irinotecan	0	0	0	0	10.3	8.3	12.3	10.8
Calcium folinate	0	0	0	0	3.3	4.2	3.9	3.4
Folinic acid, fluorouracil, oxaliplatin	0	0	0	0	1.4	4.2	1.7	1.5
Trifluridine-tipiracil	0	0	0	0	4.7	3.3	5.6	0
Cetuximab	5.4	6.3	5.4	5.4	4.2	3.3	5.0	4.4
Radiotherapy	12.9	6.3	12.9	12.9	0	0	0	0

Abbreviations: BSC, best supportive care.

The pooled FRESCO and FRESCO-2 data (21) remains the most appropriate source for clinical inputs in the cost-effectiveness analysis given that it represents a patient population that is generalisable to the UK population. For completeness, Table 32 presents results scenario analyses using clinical data from FRESCO (7) and FRESCO-2 (8) individually. In all presented scenario analysis, the severity modifier remains 1.7 vs all comparators.

Importantly, fruquintinib remains dominant when compared with regorafenib in both scenarios. The incremental NHB vs trifluridine-tipiracil is reduced from [redacted] to [redacted] using FRESCO data (7) and increases from [redacted] to [redacted] when using FRESCO-2 data (8). The incremental NHB vs BSC increases from [redacted] to [redacted] using FRESCO-2 data (8) and decreases from [redacted] to [redacted] using FRESCO data (7). The incremental NHB associated with fruquintinib vs comparators is robust to trial choice. As expected, the base case incremental NHB results, which are based on the pooled FRESCO and FRESCO-2 data (21), lie between the results associated with FRESCO and FRESCO-2 data individually (7, 8).

Table 32: FRESCO and FRESCO-2 data – scenario analysis results

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
vs regorafenib					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FRESCO data only (23)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FRESCO-2 data only (24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs trifluridine-tipiracil					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FRESCO data only (23)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FRESCO-2 data only (24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FRESCO data only (23)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
FRESCO-2 data only (24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Incremental QALYs have been calculated assuming a 1.7x severity multiplier as requested in Question B13.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OS, overall survival; PFS, progression-free survival.

Health Related Quality of Life and Utilities

B5. Document B, Section B.2.6.2.3, Figures 9 and 10, and section B.3.5.1 Figure 46: The EAG note that, at cycle 4, the least squares mean change from baseline in the QLQ-C30 and EQ-5D-5L was less for placebo (figures 9 and 10). Similarly, the mean EQ-5D-3L utility score was higher for placebo (figure 46). Please comment on the likely reasons for this result. Is this likely due to the relatively small patient numbers in the placebo group for Cycle 4 (n=30 and n=10)?

Data on HRQoL were collected using the European Organisation for Research and Treatment of Cancer – Core Quality of Life (EORTC QLQ-C30) and EuroQol five-dimension five-level (EQ-5D-5L) questionnaires. Assessments of QLQ-C30 and EQ-5D-5L were conducted at baseline (generally during screening) and on Day 1 of subsequent treatment cycles until treatment was discontinued.

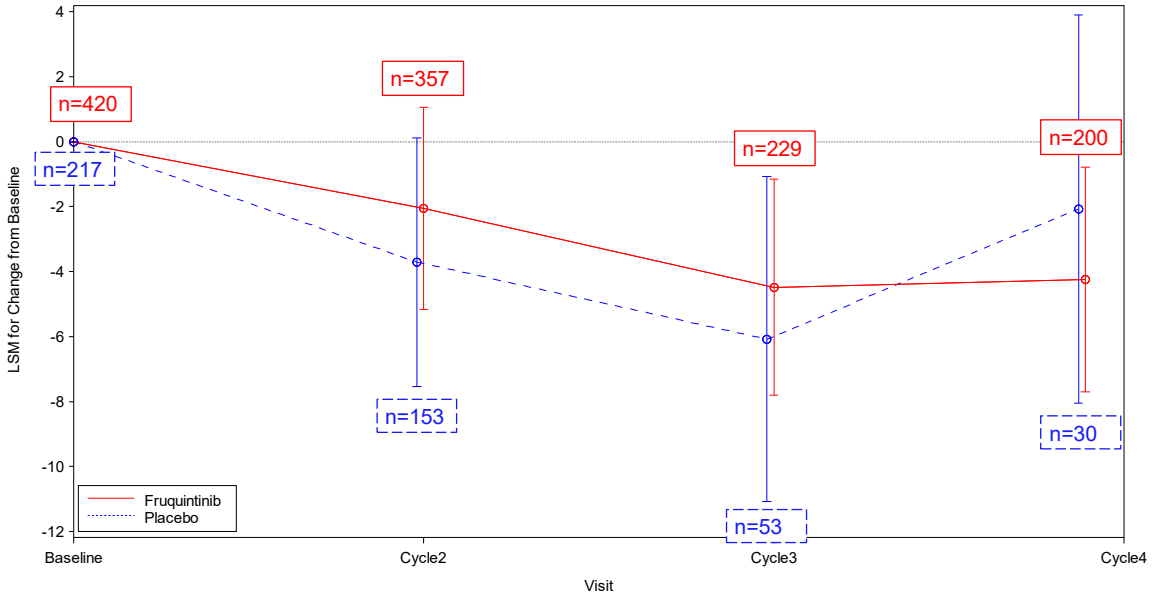
It is worth noting that the median number of cycles for the FRESCO-2 trial (8) was n=3.0 (Q1, Q3: 2.0, 6.0) for the fruquintinib arm and n=2.0 (Q1, Q3: 1.0, 3.0) for the placebo arm.

Consistent with the number of patients who remained on treatment over the course of the study, the completion rate for both EORTC QLQ-C30 and EQ-5D-5L questionnaires at the start of each cycle progressively decreased over time, with the rate of decrease greater in patients in the placebo arm vs the fruquintinib arm. As highlighted, the number of patients in the placebo arm by Cycle 4 was only n=30 (Figure 20, QLQ-C30 and Figure 21, EQ-5D-5L). In comparison, the patient numbers reported for the fruquintinib arm at Cycle 4 was n=200 (Figure 20, QLQ-C30) and

n=201 (Figure 21, EQ-5D-5L). Likewise, for the mean EuroQol five-dimension three-level (EQ-5D-3L), the number of patients at Cycle 4 was only n=26 for placebo vs n=193 for fruquintinib (Figure 24 – see also Document B, Section B.3.5.2, Figure 46). The number of patients at each visit for the observed EQ-5D-3L plot (Figure 22) are lower because they were stratified into pre-progressed disease (PD) and post-PD visits. For instance, the number of patients at cycle 4 is only n=26 and n=193 for placebo and fruquintinib, respectively, because some patients have progressed by Cycle 4 or were censored for progression status.

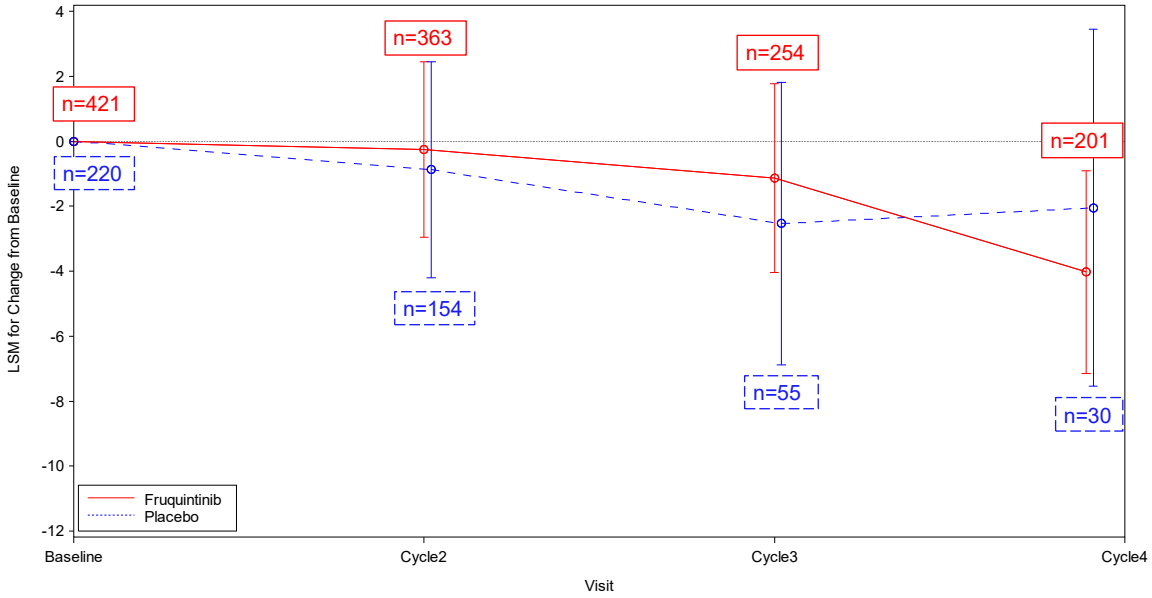
The EAG's observation regarding the Cycle 4 results being influenced by the small patient numbers in the placebo arm is valid. The reduced sample size for the placebo arm, influenced by factors such as disease progression and mortality, likely resulted in fewer patients completing questionnaires, particularly from Cycle 4 onwards. Consequently, the small sample size introduces increased uncertainty into the data from that time point, making the results at later treatment cycles less robust compared to earlier cycles. Furthermore, it's plausible that patients remaining on placebo at Cycle 4 may have a less severe disease trajectory, potentially biasing Quality of Life (QoL) assessments towards more favourable outcomes. However, it's essential to acknowledge the inherent challenges in drawing firm conclusions from the data, given the limited number of patients involved.

Figure 20: Least squares mean change from baseline: QLQ-C30 Global Health Status – FRESCO-2, ITT population



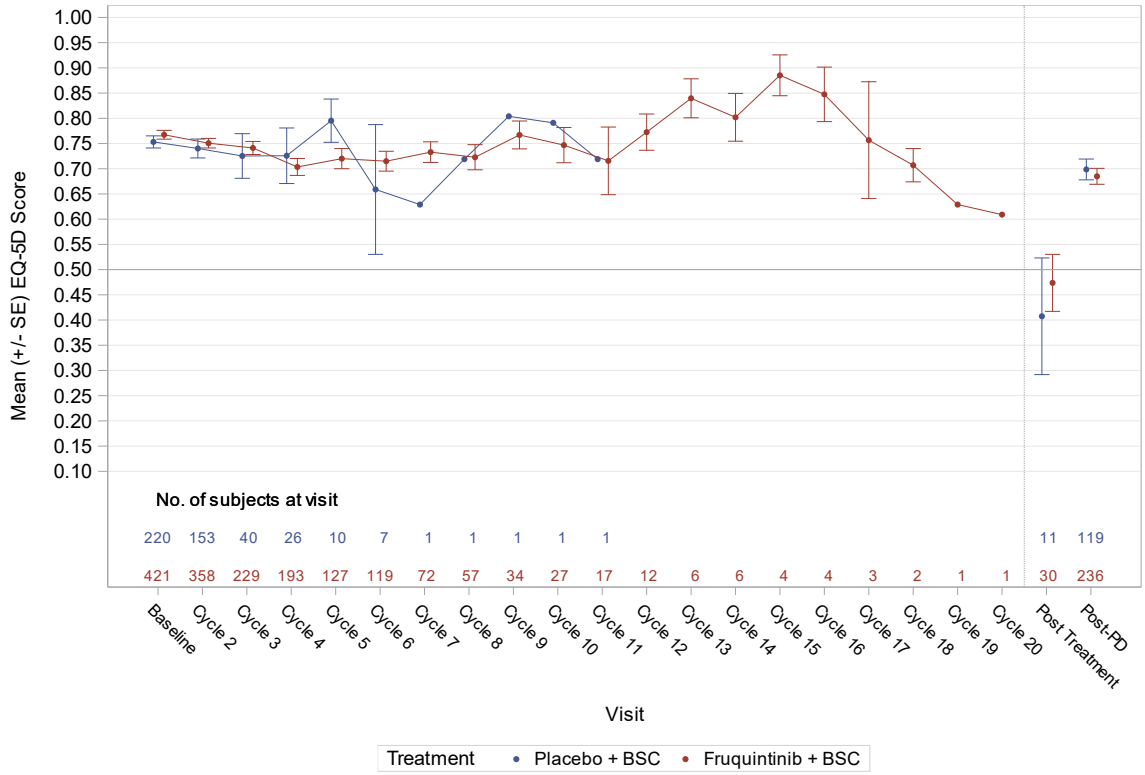
Source: FRESCO-2 figures (25).
Abbreviations: ITT, intention-to-treat; LSM, least squares mean; QLQ-C30, Core Quality of Life questionnaire.

Figure 21: Least squares mean change from baseline: EQ-5D-5L VAS – FRESCO-2, ITT population



Source: FRESCO-2 figures (25).
Abbreviations: EQ-5D-5L, EuroQol five-dimension five-level; ITT, intention-to-treat; LSM, least squares mean; VAS, visual analogue score.

Figure 22: Mean EQ-5D-3L score by visit



Abbreviations: BSC, best supportive care; EQ-5D-3L, EuroQol five-dimension three-level; PD, progressed disease; SE, standard error.

B6. Document B, Section B.3.5.1, P150, Figure 46: Please clarify if only the post-PD EQ-5D scores (n= 119 for placebo and n = 236 for fruquintinib) were used to derive the PD utility value? It is noted there is also a post-treatment visit in figure 46 (n=11 and n = 30). Were these data also included to derive the PD utility value?

Only the post-PD EQ-5D scores (n= 119 for placebo and n = 236 for fruquintinib) were used to derive the PD utility value. Patients who contributed a post-treatment visit score (n=11 for placebo and n=30 for fruquintinib) were not considered progressed and were not used to inform the PD utility value. However, these patients were still included in the utility analysis by assigning their visit to the next treatment cycle, for example for a patient who had a Cycle 4 visit and then a post-treatment visit, the post-treatment visit was treated as a 'Cycle 5' pre-progression visit.

B7. Document B, Section B.3.5.4, P155: The EAG note that the duration of adverse events is obtained from TA866, for the assessment of regorafenib. Please clarify whether data on the duration of adverse events are also available from the FRESCO studies. If these data are available, please provide

a table with duration of each adverse event and include a scenario analysis using the FRESCO specific data in the economic model.

As discussed in Document B Section B.3.5.4, clinicians at the UK market access advisory board (2) advised that the majority of adverse events (AEs) resolve soon after onset (two to 14 days) and therefore an average of one-week AE duration was considered appropriate for most AEs included in the model. This approach is also aligned with that taken in TA866 (3) and TA405 (4). A three-week duration was assumed for diarrhoea and a 0.5-week duration was assumed for decreased appetite based on clinical opinion, as highlighted in Document B (Section B.3.5.4).

However, data on mean duration of resolved AEs are available from the pooled FRESCO and FRESCO-2 studies and have been explored in the model for the purpose of the requested scenario analysis. These data are outlined in Table 33 and Table 34 for Grade ≥3 AEs and Grade 1-2 treatment-related treatment emergent adverse events (TEAEs), respectively. Data are presented separately for fruquintinib and BSC. The duration of AEs is calculated as the duration for resolved AEs, defined as the time (weeks) from AE start date to AE end date. AEs that are not resolved or those with a missing AE end date are not included in this analysis, as a mean duration could not be generated for these events. Where mean AE duration data was not estimable, the base case assumptions (one-week duration for the majority of AEs) have been maintained.

Table 33: Grade ≥3 treatment-related TEAEs mean durations (Pooled FRESCO and FRESCO-2)

Adverse event	Fruquintinib (N=734)		BSC (N=367)	
	n‡	Mean duration (SD)	n‡	Mean duration (SD)
Anaemia	0	1.00†	4	1.79 (1.99)
Asthenia	16	12.57 (11.64)	0	1.00†
Diarrhoea	22	3.97 (5.74)	0	3.00†
Fatigue	7	21.02 (10.51)	0	1.00†
Hand foot syndrome/palmar-plantar erythrodysasthesia	56	9.75 (9.05)	0	1.00†
Hypertension	61	6.04 (7.01)	3	1.00 (0.52)
Increased aspartate aminotransferase	1	0.71 (NE)	1	2.14 (NE)
Blood bilirubin increased	0	1.00†	0	1.00†
Leukopenia	1	1.00 (NE)	0	1.00†
Neutropenia	0	1.00†	1	0.43 (NE)
Rash	-	1.00†	-	1.00†
Thrombocytopenia	2	20.43 (11.72)	1	3.86 (NE)
Lymphopenia	-	1.00†	-	1.00†
Proteinuria	10	5.57 (4.87)	0	1.00†
Anorexia	-	1.00†	-	1.00†
Decreased appetite	8	7.34 (7.91)	0	0.50†
Febrile neutropenia	-	1.00†	-	1.00†
Mucositis	-	1.00†	-	1.00†
Hypophosphataemia	-	1.00†	-	1.00†
Lipase level increased	0	1.00†	0	1.00†

†Where AE duration information was not available from the pooled FRESCO and FRESCO-2 studies, the base case assumptions for duration have been maintained

‡Unresolved AEs are not considered in this scenario analysis, therefore the reported n for each event will not necessarily match the number of events in Table 42 of Document B

Abbreviations: BSC, best supportive care; NE, not estimable; SD, standard deviation; TEAE, treatment emergent adverse event.

Table 34: Grade 1-2 treatment-related TEAEs mean durations (pooled FRESCO and FRESCO-2)

Adverse event	Fruquintinib (N=734)		BSC (N=367)	
	n‡	Mean duration (SD)	n‡	Mean duration (SD)
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Anorexia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Fever	[redacted]	[redacted]	[redacted]	[redacted]
Hand-foot syndrome/ palmar-plantar erythrodysasthesia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Oral Mucositis	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Weight loss	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Voice changes	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Increased alanine aminotransferase	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]
Hyperbilirubinaemia	[redacted]	[redacted]	[redacted]	[redacted]
Increase in alkaline phosphatase	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood thyroid stimulating hormone increased	[redacted]	[redacted]	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]

†Where AE duration information was not available from the pooled FRESCO and FRESCO-2 studies, the base case assumptions for duration have been maintained

‡Unresolved AEs are not considered in this scenario analysis, therefore the reported n for each event will not necessarily match the number of events in Table 2 of Appendix F

Abbreviations: BSC, best supportive care; TEAE, treatment emergent adverse event.

As a mean duration was not available for all AEs in the model, and many AEs are associated with high uncertainty in the mean duration estimates (SD), the company considers it most appropriate to maintain the base case assumption of a one-week duration for most AEs, aligning with the committee preferred base case in TA866 (3), and clinical opinion that the majority of AEs would resolve within two to 14 days of onset. However, for completeness, Table 35 presents results of a scenario analysis using pooled FRESCO and FRESCO-2 clinical data (21) for AE durations in the cost-effectiveness model for fruquintinib and BSC. Mean AE durations for regorafenib and trifluridine-tipiracil in this scenario analysis are assumed to be equivalent to those of fruquintinib.

Importantly, fruquintinib remains dominant when compared with regorafenib, with the incremental NHB remaining unchanged when using the mean AE duration data from the pooled FRESCO and FRESCO-2 trials (21). The incremental NHB vs trifluridine-tipiracil also remains unchanged. The incremental NHB vs BSC decreases from [redacted] to [redacted] when using the mean AE duration data.

Table 35: Pooled FRESCO and FRESCO-2 AE duration data – scenario analysis results

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
vs regorafenib					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean AE duration data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs trifluridine-tipiracil					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean AE duration data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean AE duration data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Incremental QALYs have been calculated assuming a 1.7x severity multiplier as requested in Question B13.

Abbreviations: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality adjusted life years.

B8. Document B, Section B.3.5.5, P158: Related to question B6 above, please clarify how the numbers of patients and observations available for analysis for Figure 46 compare with the patient numbers and number of observations described in the text above Table 48 (n= 113 for placebo and n=213 for fruquintinib).

The data in Figure 22 (see also Document B, Figure 46) of the Company Submission relate to the observed EQ-5D-3L scores in patients with a non-missing baseline value. Of this population, 236 and 119 patients had a post-PD EQ-5D visit in the fruquintinib and BSC arms, respectively. Patients were carried forward for inclusion in the utility analysis if they had both a non-missing baseline value and a non-missing post-baseline value. Of patients with a non-missing baseline value, and at least one non-missing post-baseline value, 166 patients (represented by 213 observations) and 96 patients (represented by 113 observations) experienced a progression event in the fruquintinib and placebo arms, respectively.

A breakdown of the number of patients in the analysis is presented in Table 36.

Table 36: Patients included in utility analysis

	Fruquintinib + BSC (N=461)	Placebo + BSC (N=230)	Overall (N=871)
No. of patients with baseline or post-baseline value, n (%)	453 (98.3)	229 (99.6)	682 (98.7)
No. of patients with non-missing baseline value, n (%)	421 (91.3)	220 (95.7)	641 (92.8)
No. of patients with at least one non-missing post-baseline value, n (%)	404 (87.6)	181 (78.7)	585 (84.7)
No. of patients with non-missing baseline value and at least one non-missing post-baseline value, n (%)	372 (80.7)	172 (74.8)	544 (78.7)
No. of non-safety patients, n (%)	1 (0.2)	2 (0.9)	3 (0.3)

Abbreviations: BSC, best supportive care.

Resource use and costs

B9. Document B, Section B.3.6.2.1, P162: In relation to the relative dose intensity (RDI), the EAG note that the fruquintinib RDI is applied to all treatments on the basis that in TA866 the same RDI was preferred and that it reflected the source of efficacy data for fruquintinib. However, the EAG note that the RDIs used in the economic model do not reflect the efficacy data for regorafenib or trifluridine-tipiracil. Please provide scenario analyses applying

treatment-specific RDIs where available (e.g., using CORRECT and CONCUR data, with an assumption that regorafenib RDI is applied to trifluridine-tipiracil if no treatment specific data are available).

In both FRESCO and FRESCO-2 (23, 24), relative dose intensity (RDI) was defined as the dose intensity (mg/day) / planned dose intensity (mg/day). The planned dose intensity was (5 mg × 21) / 28 = 3.75 mg/day, as per the study protocol. In both studies, drug interruption and cycle delay were not taken into account in the derivation of RDI.

In TA866 (3), the committee preferred the use of an equal RDI applied to both treatments, regorafenib and trifluridine-tipiracil, as opposed to modelling RDI based on different sources. This was likely to ensure that a consistent definition of the RDIs was applied: cycle delay and dose reduction were modelled separately for trifluridine-tipiracil in TA405 (4), whereas they were combined in the RDI estimates in CONCUR and CORRECT (10, 11). The committee concluded that both dose delay and dose reduction should be used to estimate RDI, and that it was appropriate to derive this RDI from the pooled CORRECT and CONCUR data (10, 11). The equal RDI assumption was supported by RWE that showed similar dose reduction (not accounting for dose delay) between treatments.

To ensure consistency in RDI definition and in alignment with the committee preferred assumptions in TA866 (3), the company maintain that equivalent RDIs should be applied to fruquintinib, regorafenib, and trifluridine-tipiracil.

RDI estimates based on pooled trial data to match the efficacy data for regorafenib and trifluridine-tipiracil are not available as this data is redacted in TA866 (3). However, for completeness, a scenario analysis is presented in Table 37 that uses the available RDI data from CORRECT (78.9%) and RECOURSE (89%) for regorafenib and trifluridine-tipiracil, respectively (10, 12). RDI data were unavailable for other regorafenib and trifluridine-tipiracil trials. Fruquintinib remains dominant compared with regorafenib, the NHB vs trifluridine-tipiracil is decreased slightly from [redacted] to [redacted].

Table 37: RDI scenario analysis results

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
vs regorafenib					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI from respective trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs trifluridine-tipiracil					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI from respective trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RDI from respective trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Incremental QALYs have been calculated assuming a 1.7x severity multiplier as requested in Question B13.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; RDI, relative dose intensity.

B10. Document B, Section B.3.6.2.1, P162: Please comment further on the likely reasons for the substantially lower RWE RDIs for regorafenib and trifluridine-tipiracil of 54% and 48% respectively compared to the available trial evidence? Is it assumed that fruquintinib RDI would be similarly low in UK clinical practice? Please provide additional scenario analyses testing lower and differential RDIs that may be observed in UK clinical practice.

The figures of 54% and 48% as per the TA866 final appraisal determination (FAD) (15), are sourced from Nakashima et al (2020) (26). However, it's crucial to recognise that these percentages are not estimates of RDI, rather the proportion of patients who had a dose reduction. When comparing these values to the definition of RDI for FRESCO/FRESCO-2 trials as mentioned earlier (see response to clarification question B9), a clear disparity emerges. The RDI in FRESCO/FRESCO-2 trials refers to a specific set of guidelines tailored to the trial's parameters and objectives. Therefore, it's not appropriate to utilise the Nakashima et al (2020) data to inform the RDI within the model, as they serve different purposes and contexts.

However, it is likely that the RDI for regorafenib, trifluridine-tipiracil and fruquintinib would be lower in clinical practice than observed in clinical trials, as patients in RWE studies are often less fit compared to trial populations due to strict clinical trial inclusion criteria and are therefore less able to tolerate higher treatment doses. As discussed in Document B, Section B.2.1. of the Company submission, a clinical SLR was conducted to identify all available evidence on the efficacy, safety and HRQoL in patients with mCRC who have been previously treated with or are not considered candidates for available therapies. Of the identified publications, seven RWE studies (27-33) reported RDI data for regorafenib (Table 43). Of these, six studies (27-31, 33) reported median RDI ranging from 45% to 80% (Table 43), and two studies reported mean RDI of 54% (32) to 71% (29) (Table 43). Seven RWE studies (31, 32, 34-38) reported RDI data for trifluridine-tipiracil (Table 44). Of these, five studies (31, 34-37) reported median RDI ranging from 57% to 100% (Table 44), one study reported mean RDI of 83% (32) (Table 44), and one study (38) reported the number of participants with median RDI <80%, 80 to 100%, 100% or >100%, with the majority reporting median RDI 100% (Table 44). One RWE study (39) reported median RDI of 85.3% for fruquintinib (Table 45). These data demonstrate that although RDI could be expected to be lower in real-world practice, there is substantial variation and uncertainty on the most appropriate value. The company maintain that equivalent RDIs should be applied to fruquintinib, regorafenib, and trifluridine-tipiracil, and that the pooled FRESCO and FRECSO-2 data is the most appropriate source for RDI.

RDI data based on RWE for fruquintinib were available from a prospective, multicentre, Phase IV study evaluating real-world safety of fruquintinib in China, as reported by Li et al (39). The median RDI (85.3%), was similar to RDI from the pooled FRESCO and FRESCO-2 data (89.6%), demonstrating that fruquintinib may be similarly well-tolerated in clinical practice as it is in the clinical trial environment. Furthermore, fruquintinib has been used in practice in the US since it was approved by the US FDA in November 2023 for treatment of adult patients with 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 (40). Although RWE from the first five months of fruquintinib use in the US is limited, initial reports indicate that approximately [redacted] of patients have required dose reductions, so an RDI in line with the pooled FRESCO

and FRESCO-2 data or Li et al (2023; Phase IV study) could be expected in real-world clinical practice.

A scenario analysis is presented in Table 38 applying the RWE RDI from Li et al (85.3%) to fruquintinib, regorafenib and trifluridine-tipiracil. As discussed in the response to question B9, it was considered most appropriate to apply the same RDI to all active treatments to account for differing definitions of RDI across studies. Fruquintinib remains dominant compared with regorafenib, the NHB vs trifluridine-tipiracil increased from [redacted] to [redacted].

Table 38: Scenario analysis – dose intensity from RWE

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
vs regorafenib					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
85.3% RDI for all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs trifluridine-tipiracil					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
85.3% RDI for all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
85.3% RDI for all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Incremental QALYs have been calculated assuming a 1.7x severity multiplier as requested in Question B13.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality adjusted life years; RDI, relative dose intensity; RWE, real world evidence; vs, versus.

B11. Document B, Section 3.6.5, table 60: Subsequent therapies presented in Table 60 may be more reflective of UK clinical practice, but the proportion receiving treatment may be lower than 20%. Please provide sensitivity analysis assuming 10% of patients receive subsequent anti-cancer treatment

to illustrate the impact of uncertainty surrounding post-progression treatment costs on results.

The results of scenario analyses assuming that only 10% of patients in the fruquintinib and trifluridine-tipiracil arms receive subsequent therapy, with the proportions of each subsequent therapy as per the UK clinical opinion used in the base case, are presented in Table 39. It was assumed that 5% of patients receive subsequent therapy in the regorafenib arm, as per the base case. Fruquintinib remains dominant when compared with regorafenib, with the incremental NHB remaining unchanged. The incremental NHB vs trifluridine-tipiracil remained unchanged. The incremental NHB vs BSC increased from [redacted] to [redacted] at a willingness to pay (WTP) threshold of £30,000 per quality adjusted life year (QALY).

Table 39: Proportion of patients receiving subsequent therapy scenario analysis results

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
vs regorafenib					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy proportions from clinical opinion + 10% of patients receiving subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs trifluridine-tipiracil					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy proportions from clinical opinion + 10% of patients receiving subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy proportions from clinical opinion +	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
10% of patients receiving subsequent therapy					

†Incremental QALYs have been calculated assuming a 1.7x severity multiplier as requested in Question B13.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALYs, quality adjusted life years; RE, random effects; vs, versus.

B12. Document B, Section 3.6.5, P166. The EAG note that subsequent treatment costs are incurred in the model over a duration of one-week only. Please provide a clinical justification for restricting post-progression treatment cycles to one-week only, particularly given that chemotherapy cycles are often of longer duration. Please provide scenario analysis within the model that reports results for a 2-month (approx. 8 weeks) duration of subsequent treatments.

Patients with mCRC who have received at least two prior therapies have a poor prognosis and face substantial disease and treatment-related burden. Therefore, to reflect the poor prognosis of patients who progress to fourth-line therapy and beyond, a one-week subsequent treatment duration was considered suitable. This also aligns with the committee's preferred approach in both TA405 and TA866 (3, 4).

Given this poor survival, there is uncertainty on the subsequent therapy duration, so two scenario analyses are presented, assuming an eight-week or four-week subsequent treatment duration (Table 40). Fruquintinib remains dominant when compared with regorafenib, with an increase in the incremental NHB from [redacted] to [redacted] when considering an eight-week duration and an increase from [redacted] to [redacted] when considering a four-week duration, at a WTP threshold of £30,000 per QALY. The incremental NHB vs trifluridine-tipiracil is increased from [redacted] to [redacted] and [redacted] to [redacted] when assuming an eight-week and four-week duration, respectively. The incremental NHB vs BSC is reduced from [redacted] to [redacted] and from [redacted] to [redacted] when assuming an eight-week and four-week duration respectively.

Table 40: Subsequent therapy duration scenario analysis results

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at (£20,000/ QALY WTP threshold)	Incremental NHB at (£30,000/ QALY WTP threshold)
vs regorafenib					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy duration: 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy duration: 4 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs trifluridine-tipiracil					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy duration: 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy duration: 4 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC					
Submitted base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy duration: 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy duration: 4 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Incremental QALYs have been calculated assuming a 1.7x severity multiplier as requestion in Question B13.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality adjusted life years; vs, versus.

Results

B13. Document B, Section 3.11 and 3.12, Results Tables: Please provide the main results tables in the submission with the company preferred severity weighting applied to incremental QALYs. The EAG appreciates that overall conclusions are similar to providing incremental NHB at £34,000 and £51,000

reflecting 1.2 and 1.7 weightings respectively. However, there is a subtle difference as the reported approach assumes an unweighted threshold of £30,000 rather than a usual threshold range of £20,000 to £30,000.

For clarification, the base case results in Table 72 of the company submission presented NHB at a willingness-to-pay threshold of £34,000 and £51,000 as this is equivalent to applying a 1.7x severity modifier to a threshold of £20,000 and £30,000, respectively. Results are presented in Table 41 and Table 42 with the 1.7x severity modifier applied to incremental quality-adjusted life years (QALY). Results presented throughout this clarification question response document reflect the 1.7x severity modifier being applied to incremental QALYs, as opposed to applying the modifier to the threshold as per the original Company submission.

Table 41: Base case results (fully incremental analysis) – PAS price, including 1.7 x severity modifier

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	–	–	–	–
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 42: Base case results (pairwise analysis) – PAS price, including 1.7 x severity modifier

Technologies	Total costs (£)	Total QALYs	fruquintinib vs comparator						
			Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALYs including 1.7 x severity modifier	Pairwise ICER	Incremental NHB at £20,000 WTP threshold	Incremental NHB at £30,000 WTP threshold
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	–	–	–		–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness to pay.

Section C: Textual clarification and additional points

C1. Reference pack. The reference pack submitted by the company contains sub-folders for FRESCO and FRESCO-2 data on file. The EAG is unable to access documents in these sub-folders, namely CSRs, SAPs and protocols. Please provide further copies of these documents.

The documents requested are provided in the smaller reference pack, which has been submitted alongside this document:

- FRESCO: protocol (41), statistical analysis plan (SAP) (42), and clinical study report (CSR) (23).
- FRESCO-2: protocol (43), SAP (44), and CSR (24).

C2. Document B, Section B.3.1, P117 & Appendix G. The company submission indicates that an SLR was conducted on 23rd October 2023; however, in Appendix G it is reported that searches were conducted on the 4th of October 2023 and that the grey literature search was conducted on the 11th of October. Please clarify literature search dates.

The electronic database searches for the economic SLR were conducted on 4th October 2023, and grey literature searches were conducted on 26th October 2023.

The following corrections therefore apply:

- Section B.3.1: “An SLR was conducted on 4th October 2023 to identify economic evaluations in patients with mCRC who have been previously treated with…”
- Appendix G, Section G.1.2.9, Table 10: “Table 10: Grey literature searches (date searched 26th October 2023)”.

C3. Document B, Sections B.3.2.8.1 & B.3.3. Please check the references reported in these sections. Please confirm that the references are for the FRESCO trials rather than previous NICE guidance.

The references reported in Section B.3.2.8.1 should be to the FRESCO (Li et al., 2018 (7)) and FRESCO-2 (Dasari et al. 2023 (8)) trials and to the fruquintinib summary of product characteristics (SmPC) (45):

- "The intervention considered in this analysis is fruquintinib, which is administered orally at a recommended dose of 5 mg QD following a dosing schedule of three weeks on and one week off as per the dosing regimen received in FRESCO and FRESCO-2 (7, 8), and the anticipated marketing authorisation for fruquintinib, combined with BSC (45). Treatment with fruquintinib should be continued until disease progression or unacceptable toxicity occurs."

The references reported in Section B.3.3 should be to the FRESCO (Li et al., 2018 (7)) and FRESCO-2 (Dasari et al. 2023 (8)) trials:

- "Both large, Phase III randomised, placebo-controlled trials assessing fruquintinib in the relevant population, FRESCO and FRESCO-2, were used to inform the clinical inputs for fruquintinib and BSC in the economic model (7, 8). As discussed in Section B.2.6.3, the two trials were pooled and were used to inform modelled patient baseline characteristics, OS, PFS, and TTD for fruquintinib, OS and PFS for BSC, AE rates, RDI and subsequent therapies."

C4. Document B, Section B.3.3.2.2, P136. Please confirm that the reference to Figure 32, should be Figure 39. Please also confirm that interpretation of findings is derived from Figure 39 for PFS.

The in-text cross reference to the quantile-quantile plot for PFS should be to Figure 39 and not to Figure 32. The interpretation of findings for PFS is based on Figure 39 and is correct as reported.

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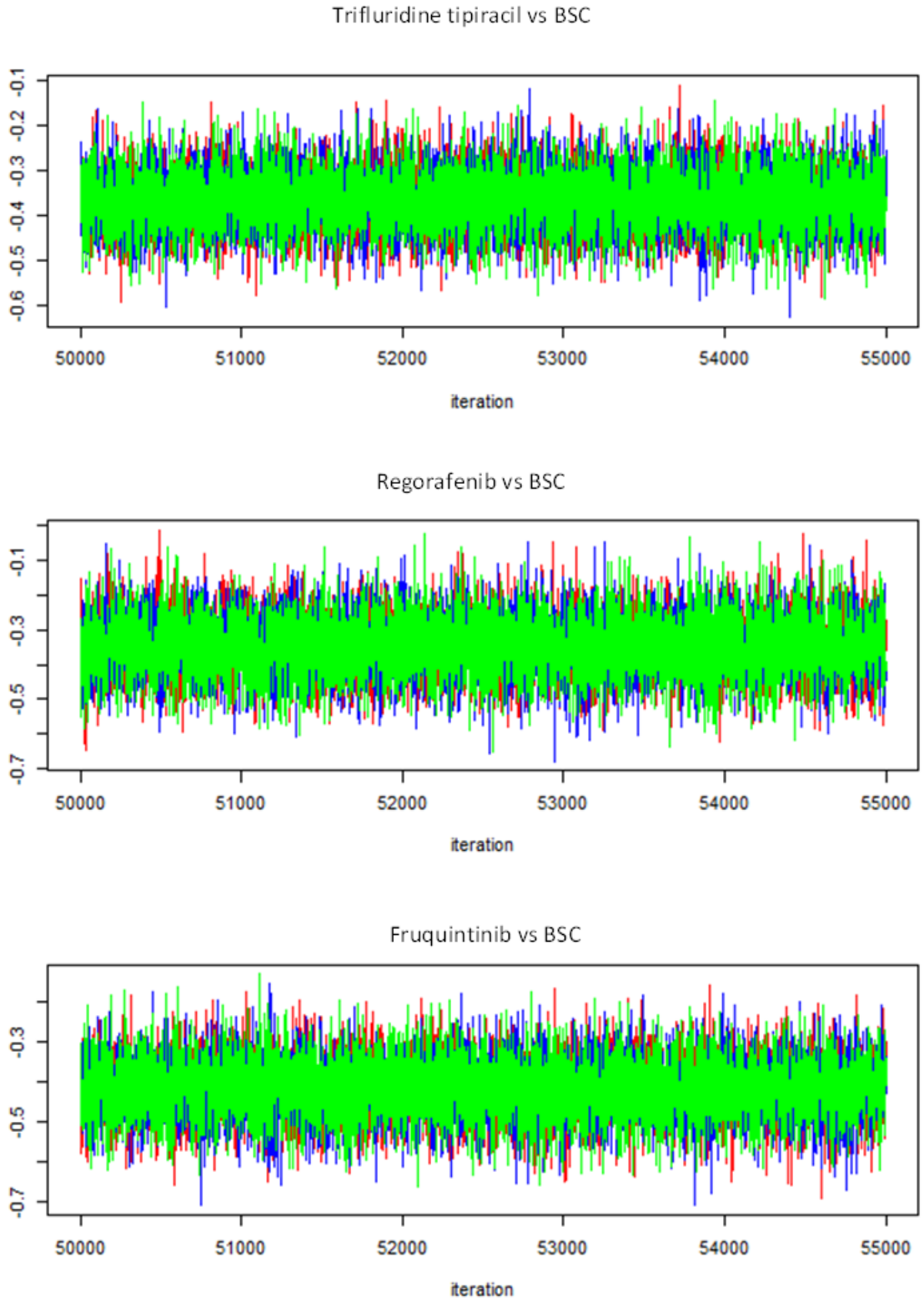
Supplementary information

Supplementary information B2

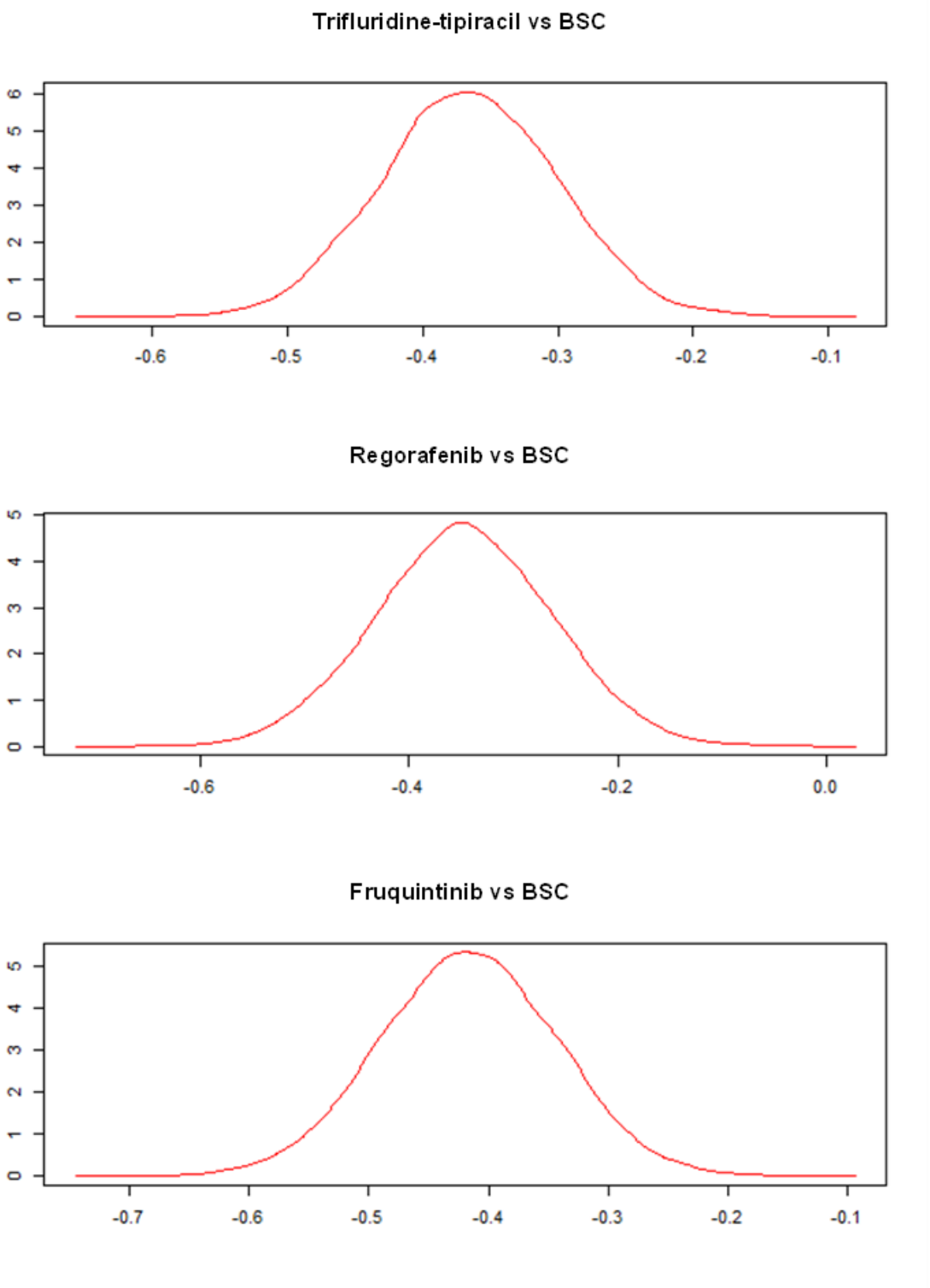
The trace plots and density plots for OS are provided in and Figure 24, respectively for FE models and in Figure 25 and Figure 26, respectively for RE models; and, the trace plots and density plots for PFS are provided in Figure 27 and Figure 28, respectively for FE models and in Figure 29 and Figure 30, respectively for RE models.

Figure 23: Base case: OS fixed effects – trace plot



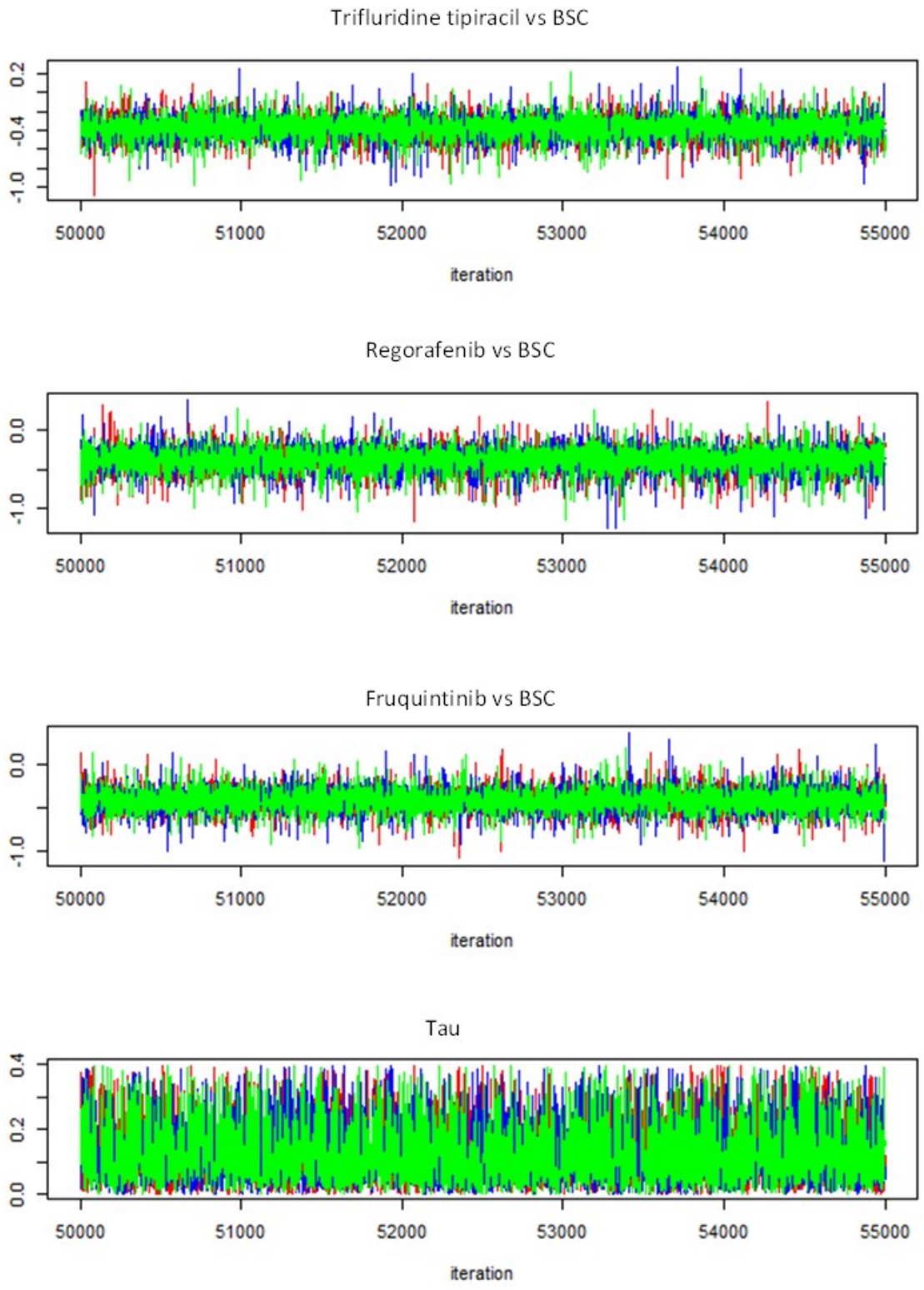
Note: Treatments were in combination with BSC and BSC was in combination with placebo.
Abbreviations: BSC, best supportive care; OS, overall survival.

Figure 24: Base case: OS fixed effects – density plot



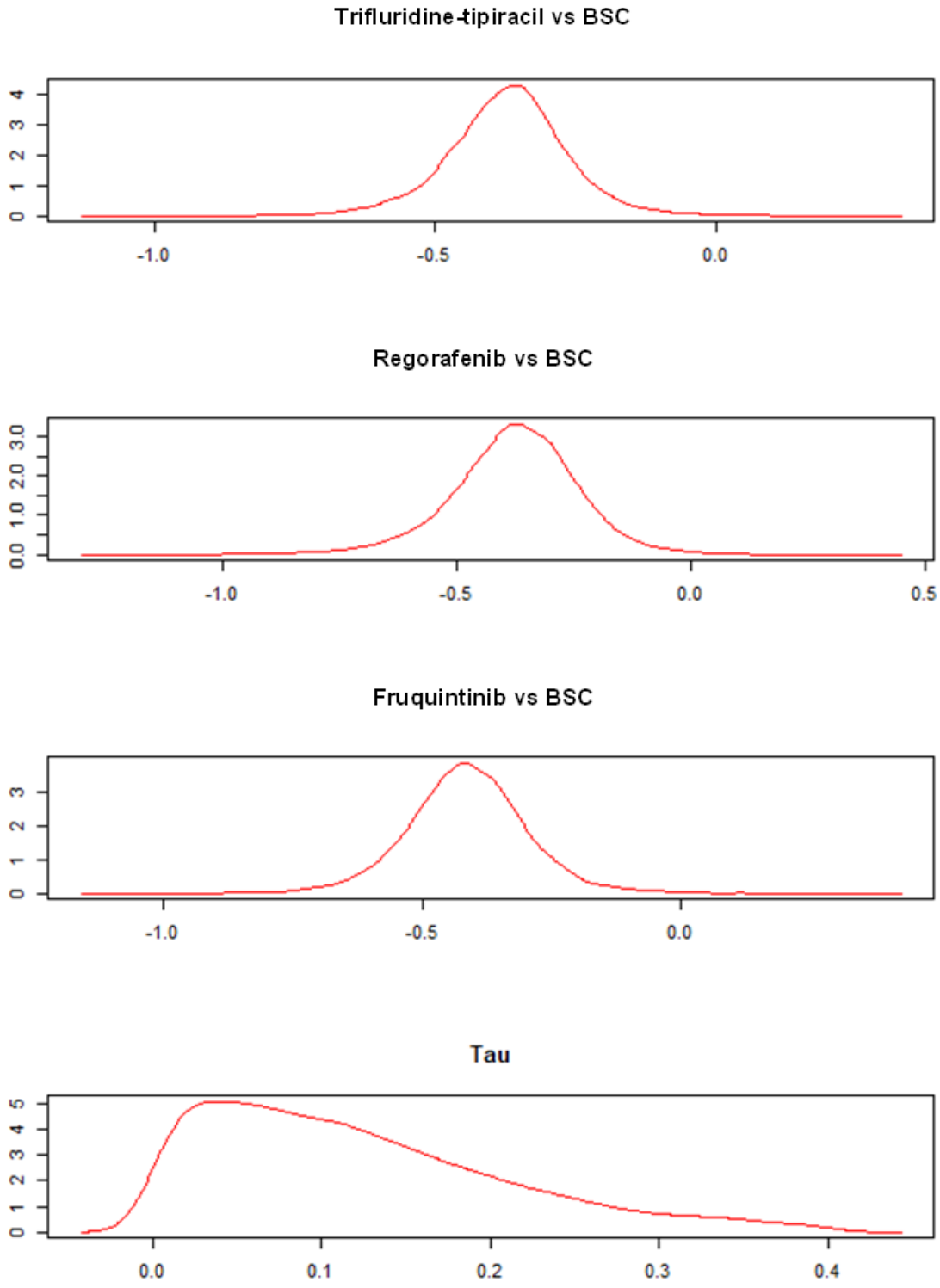
Note: Treatments were in combination with BSC and BSC was in combination with placebo.
Abbreviations: BSC, best supportive care; OS, overall survival.

Figure 25: Base case: OS random effects – trace plot



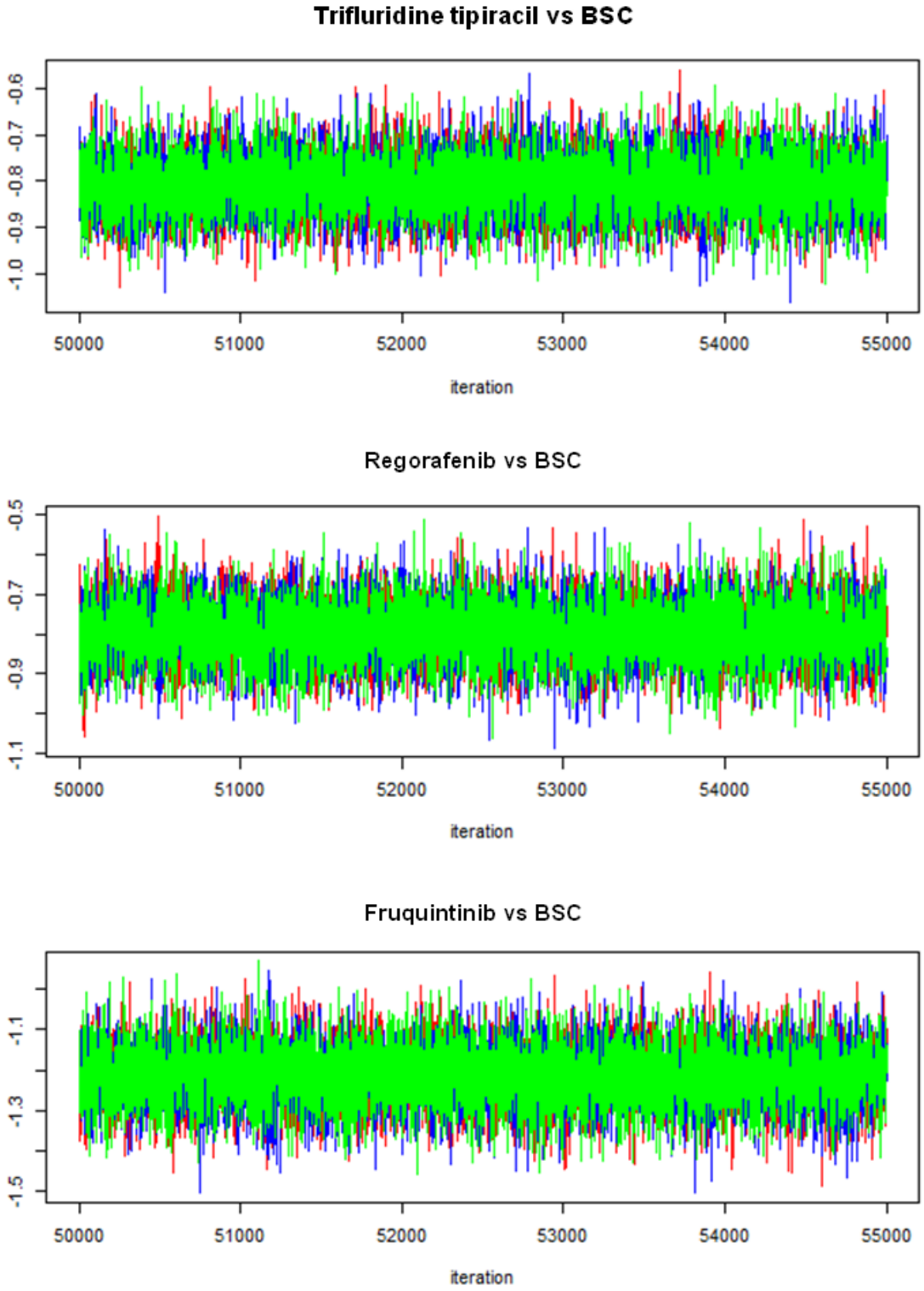
Note: Treatments were in combination with BSC and BSC was in combination with placebo.
Abbreviations: BSC, best supportive care; OS, overall survival.

Figure 26: Base case: OS random effects – density plot



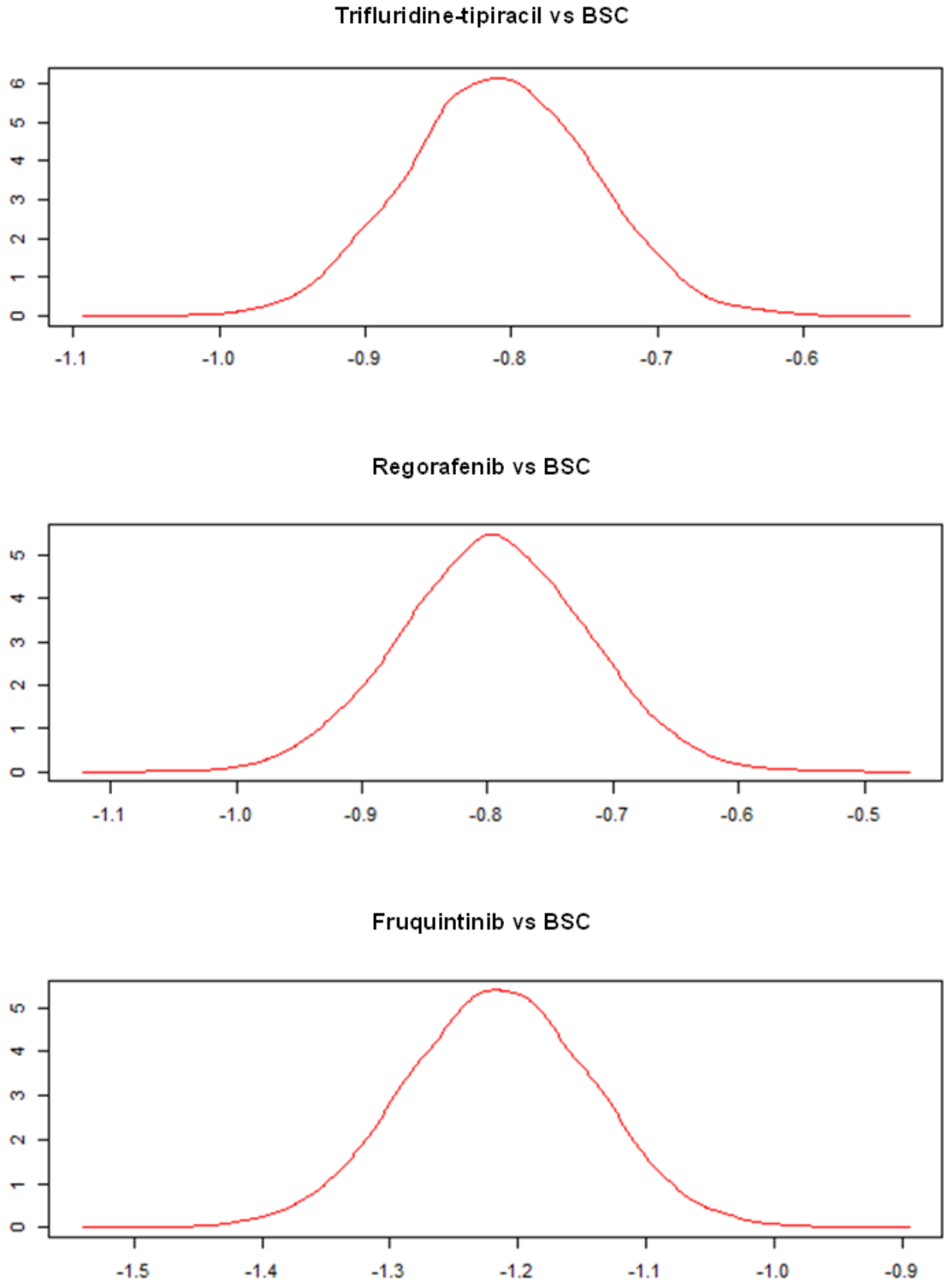
Note: Treatments were in combination with BSC and BSC was in combination with placebo.
Abbreviations: BSC, best supportive care; OS, overall survival.

Figure 27: Base case: PFS fixed effects – trace plot



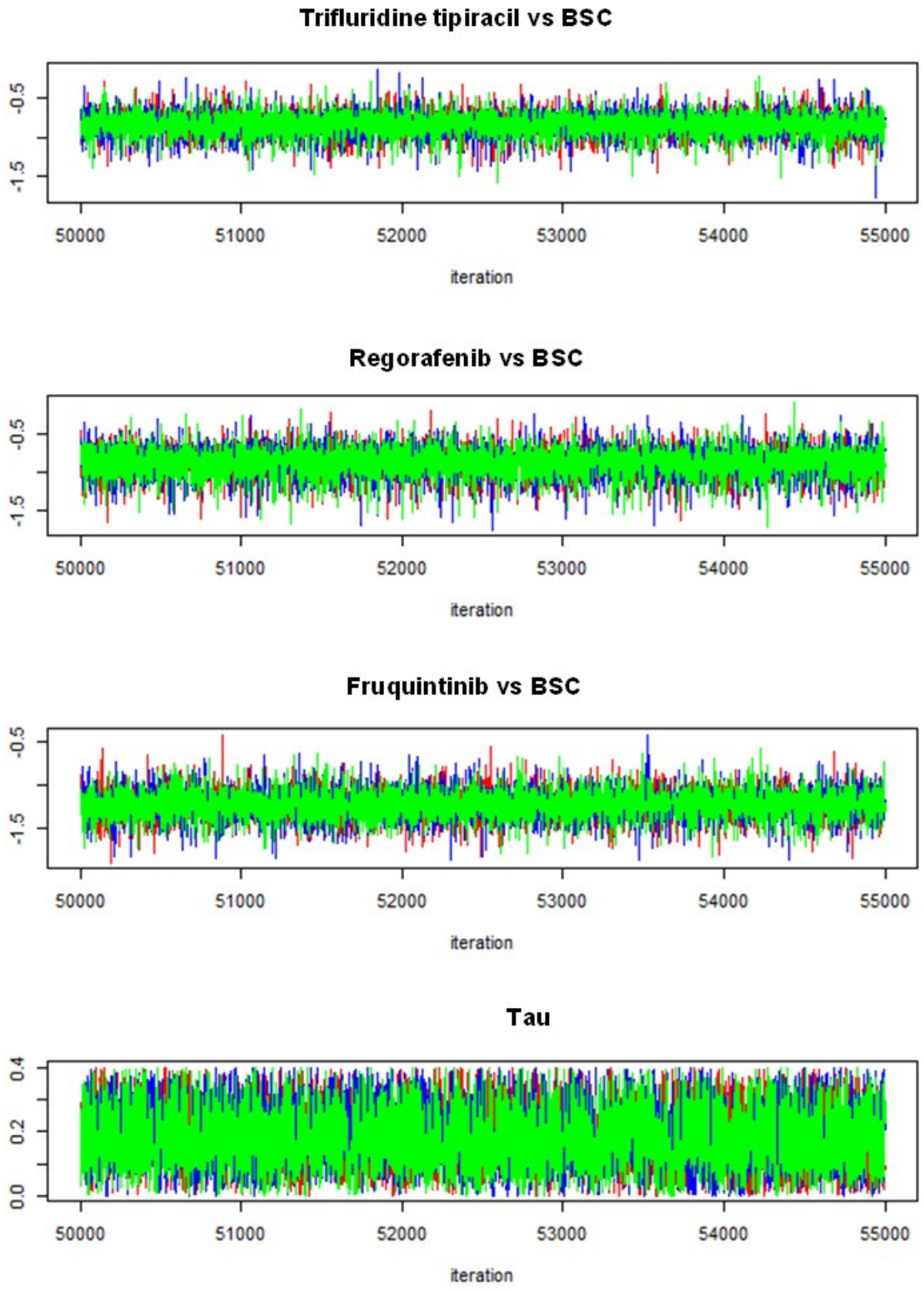
Note: Treatments were in combination with BSC and BSC was in combination with placebo.
Abbreviations: BSC, best supportive care; PFS, progression-free survival.

Figure 28: Base case: PFS fixed effects – density plot



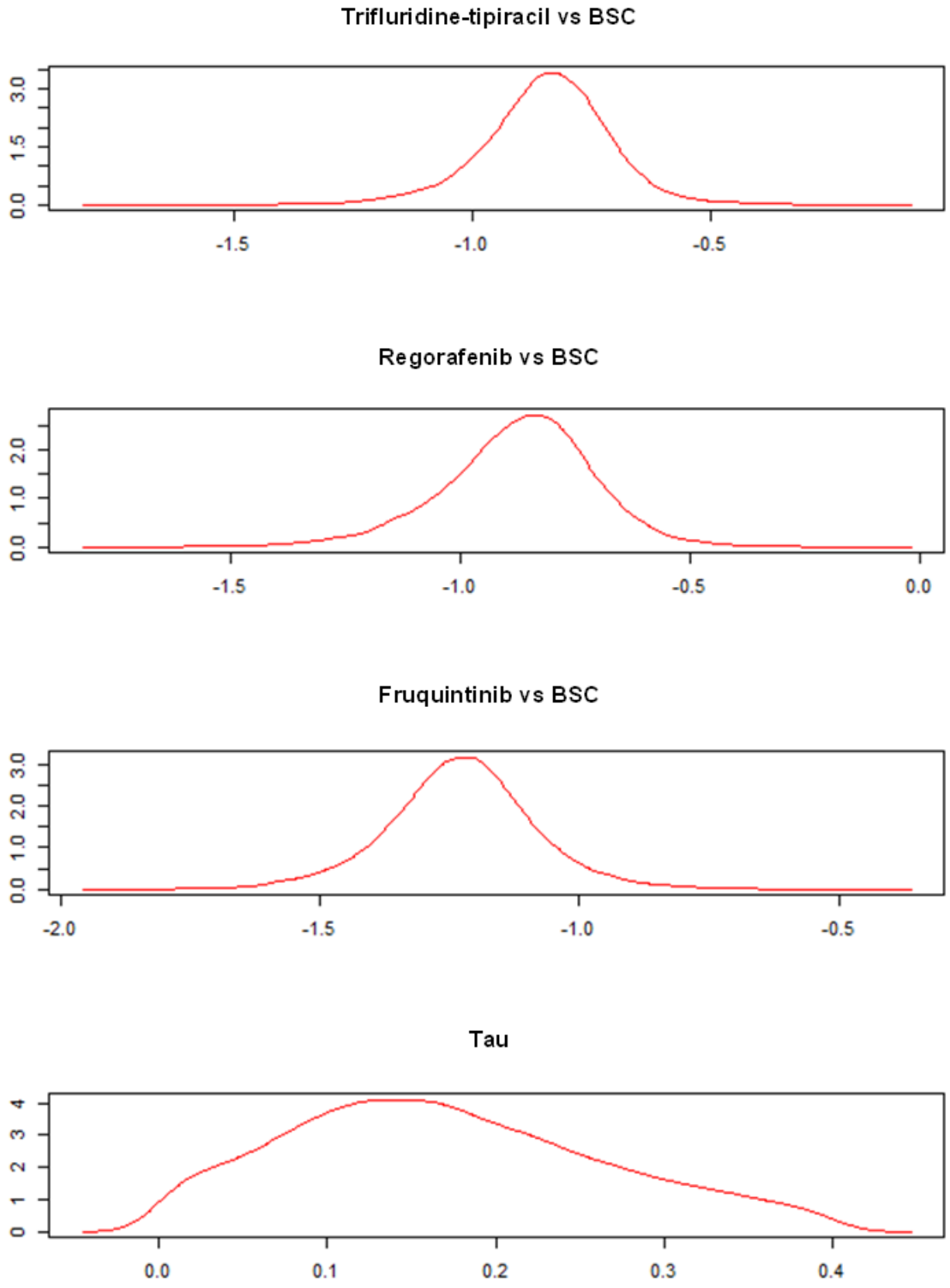
Note: Treatments were in combination with BSC and BSC was in combination with placebo.
Abbreviations: BSC, best supportive care; PFS, progression-free survival.

Figure 29: Base case: PFS random effects – trace plot



Note: Treatments were in combination with BSC and BSC was in combination with placebo.
Abbreviations: BSC, best supportive care; PFS, progression-free survival.

Figure 30: Base case: PFS random effects – density plot



Note: Treatments were in combination with BSC and BSC was in combination with placebo.
Abbreviations: BSC, best supportive care; PFS, progression-free survival.

Supplementary information B10

Table 43, Table 44, and Table 45 provide RDI data from real-world evidence studies identified in the systematic literature review for regorafenib, trifluridine-tipiracil, and fruquintinib, respectively.

Table 43: Relative dose intensity (regorafenib) as reported in real world evidence

First author, year (Study country)	N randomised/ evaluated at baseline/ completed	Study population characteristics	Treatment name and dose	Treatment schedule and cycle length (days)	Median (range) actual number of cycles	Median (range) actual treatment duration (months)	Definition of relative dose intensity	Relative dose intensity	Median follow-up
Carrato, 2019 (27) (Spain)	47/ 47/ 47	Median age (var): 81 (Range: 63 to 89); n (%) male: 26 (55.0); n (%) Asian: NR	Regorafenib 160 mg	Once daily for 21 days of a 28-day cycle	Median: 2 (range: 1 to 20), mean: 4.2	NR	(mg/day/planned total dose)	0.76 (range: 0.48 to 1.01)	10.7 months
Hirano, 2015 (28) (Japan)	NA/ 32/ 6	Median age (var): 61 (Range: 30 to 78); n (%) male: 18 (56); n (%) Asian: 32 (100)	Regorafenib at 160 mg/day	Regorafenib was administered at a dose of 160 mg/day for the first 21 days of each 28-day cycle	NR	10.9 (range: 0.6 to 51.9) weeks	No definition of RDI reported	Median: 59% (24-100%)	NR
Kato, 2023 (29) (Japan)	60/ 60/ 58	Median age (var): 68.5 (Range: 47 to 80); n (%) male: 30 (50); n (%) Asian: NR	Regorafenib, 120 mg once daily	once daily for 3 weeks (Day 1–21), followed by a 1-week of-treatment period (Day 22–28)	NR	2 (0.2 - 11)	No definition of RDI (data reported are dose intensity not RDI)	Mean (SD): 71.0% (22.6%); Median (range): 71.0% (22.6%)	NR

First author, year (Study country)	N randomised/ evaluated at baseline/ completed	Study population characteristics	Treatment name and dose	Treatment schedule and cycle length (days)	Median (range) actual number of cycles	Median (range) actual treatment duration (months)	Definition of relative dose intensity	Relative dose intensity	Median follow-up
Ogata, 2023 (30) (Japan)	NA/ 250/ 250	Median age (var): NR (NR); n (%) male: NR; n (%) Asian: NR	Regorafenib	NR	NR	NR	No definition of RDI reported (abstract only)	Period A (before May 2018): 0.549; Period B (after May 2018): 0.519	NR
Patel, 2021 (31) (USA)	NA/ 95/ 95	Median age (var): 57 (SD: 11.7); n (%) male: 52 (54.7); n (%) Asian: NR	Regorafenib, 160 mg once daily	Once daily	NR	NR	RDI was defined as the ratio of dose intensity to recommended dose where recommended dose is 35 mg/m^2 twice daily for trifluridine-tipiracil and 160 mg daily for regorafenib	Median RDI: 0.8 p-value <0.001 vs trifluridine-tipiracil	6.3
Tanaka, 2018 (32) (Japan)	20/ 20/ NR	Median age (var): 68 (Range: 57 to 78); n (%) male: 13 (65.0); n (%) Asian: 20 (100)	Regorafenib, 160 mg	Once daily on days 1-21, with 7 days of rest	NR	2.6 (0.1 to 10.8)	The planned dose intensity (DI) for each drug was defined as the total amount of drug in the entire treatment	Mean ± SD: 0.54 ± 0.21	NR

First author, year (Study country)	N randomised/ evaluated at baseline/ completed	Study population characteristics	Treatment name and dose	Treatment schedule and cycle length (days)	Median (range) actual number of cycles	Median (range) actual treatment duration (months)	Definition of relative dose intensity	Relative dose intensity	Median follow-up
							intended based on the recommended dose and schedule. Then, the relative dose intensity (RDI) for each drug was calculated as the ratio between the delivered DI and the planned DI		
Watanabe, 2021 (33) (Japan)	NA/ 60/ 60	Median age (var): 66 (range: 57 to 72); n (%) male: 34 (56.7); n (%) Asian: 60 (100)	Regorafenib, NR	Once a day on days 1–21 in a 28-day cycle	NR	NR	No definition of RDI reported	Median RDI: 0.45 (IQR: 39.2—64.1)	6 (IQR: 3.27 to 12.23)

Abbreviations: DI, dose intensity; IQR, interquartile range; NA, not applicable; NR, not reported; RDI, relative dose intensity; SD, standard deviation; var, variance

Table 44: Relative dose intensity (trifluridine-tipiracil) as reported in real world evidence

First author, year (Study country)	N randomised/ evaluated at baseline/ completed	Study population characteristics	Treatment name and dose	Treatment schedule and cycle length (days)	Median (range) actual number of cycles	Median (range) actual treatment duration (months)	Definition of RDI	Relative dose intensity	Median follow-up
Bachet, 2020 (34) (Australia, Belgium, Bulgaria, Croatia, France, Ireland, Italy, Panama, Poland, Portugal, Slovakia, Slovenia and Turkey)	793/ 793/ 793	Median age (var): 62 (range: 24 to 87); n (%) male: 475 (59.9); n (%) Asian: NR	Trifluridine-tipiracil 35 mg/m2	Twice daily on days 1–5 and 8–12 of each 28-day cycle	3 (1 - 16)	2.8 (IQR: 2.64)	No definition of RDI reported	Median: 89.9%	NR
Fujii, 2020 (35) (Japan)	NA/ 36/ 36	Median age (var): 67.5 (IQR: 59.8 to 71.2); n (%) male: 16 (44.4); n (%) Asian: 36 (100)	Trifluridine-tipiracil (35 mg/m² of body surface area)	Twice a day on days 1–5 and 8–12 in a 28-day cycle	NR	NR	No definition of RDI reported	The RDI of trifluridine-tipiracil was 0.57	NR
Hamauchi, 2017 (36) (Japan)	NA/ 95/ 95	Median age (var): 64 (range: 32 to 90); n (%) male: 55 (58)n (%) Asian: 95 (100)	Trifluridine-tipiracil 35 mg/m²	Twice daily, after breakfast and dinner, for 5 days a week with 2 days of rest for 14 days,	2 (1 to 13)	NR	(Dose intensity/planned dose intensity x 100)	RDI (dose intensity/ planned dose intensity X 100) of trifluridine-tipiracil in the first cycle was 88%	9.1 (1.4 to 16.1)

First author, year (Study country)	N randomised/ evaluated at baseline/ completed	Study population characteristics	Treatment name and dose	Treatment schedule and cycle length (days)	Median (range) actual number of cycles	Median (range) actual treatment duration (months)	Definition of RDI	Relative dose intensity	Median follow-up
				followed by a 14-day rest period (1 treatment cycle). This treatment cycle was repeated every 28 days					
Kroning, 2023 (37) (Germany)	NA/ 300/ 300	Median age (var): 67.73 (range: 33.4-90.5); n (%) male: 174 (58.0); n (%) Asian: NR	Trifluridine-tipiracil 35 mg/m2 twice daily	35 mg/m2 administered orally twice daily on days 1 to 5 and days 8 to 12 of each 28-day cycle	NR	Median (range): 2.2 (0.0-21.5)	RDI was calculated based on the recommended dose according to the current applicable version of the German SmPC of Lonsurf.	Median (range): 91.3% (15.5-118.6)	NR
Marques, 2023 (38) (Portugal)	NA/ 111/ 111	Median age (var): NR (range: 36–85); n (%) male: 59 (53.2); n (%) Asian: NR	Trifluridine-tipiracil 35 mg/m2 twice daily	Initiating dose of 35 mg/m2 twice daily, 5 days of treatment followed by a 2-day rest period	Mean (95% CI): 3.7 (3.4-4.1)	NR	(Ratio of delivered dose intensity divided by the planned dose intensity according to the summary of SmPC)	<80%: 4 (3.7) 80% to <100%: 12 (11.2) 100%: 86 (80.4) >100%: 5 (4.7) Missing 4 patients	7.7 (range 1-23)

First author, year (Study country)	N randomised/ evaluated at baseline/ completed	Study population characteristics	Treatment name and dose	Treatment schedule and cycle length (days)	Median (range) actual number of cycles	Median (range) actual treatment duration (months)	Definition of RDI	Relative dose intensity	Median follow-up
				each week for 2 weeks, and then a 14-day rest period (28-day cycle)					
Patel, 2021 (31) (USA)	NA/ 126/ 126	Median age (var): 55 (SD: 11.1); n (%) male: 57 (45.2); n (%) Asian: NR	Trifluridine-tipiracil 35 mg/m2, twice daily	Twice daily	NR	NR	RDI was defined as the ratio of dose intensity to recommended dose where recommended dose is 35 mg/m^2 twice daily for trifluridine-tipiracil and 160 mg daily for regorafenib	Median: 1.0	7.1
Tanaka, 2018 (32) (Japan)	24/ 24/ NR	Median age (var): 64 (range: 44 to 86); n (%) male: 15 (62.5); n (%) Asian: 24 (100)	Trifluridine-tipiracil 35 mg/m^2	Twice daily 5 days a week, with 2 days of rest, for 14 days, followed by a 14-day rest period	NR	3.8 (0.9 to 20.3)	The planned DI for each drug was defined as the total amount of drug in the entire treatment intended based on the recommended	Mean ± SD: 0.83 ± 0.14	NR

First author, year (Study country)	N randomised/ evaluated at baseline/ completed	Study population characteristics	Treatment name and dose	Treatment schedule and cycle length (days)	Median (range) actual number of cycles	Median (range) actual treatment duration (months)	Definition of RDI	Relative dose intensity	Median follow-up
							dose and schedule. Then, the RDI for each drug was calculated as the ratio between the delivered DI and the planned DI		

Abbreviations: CI, confidence interval; DI, dose intensity; IQR, interquartile range; NA, not applicable; NR, not reported; RDI, relative dose intensity; SD, standard deviation; SmPC, summary of product characteristics; var, variance.

Table 45: Relative dose intensity (fruquintinib) as reported in real world evidence

First author, year (Study country)	N randomised/ evaluated at baseline/ completed	Study population characteristics	Treatment name and dose	Treatment schedule and cycle length (days)	Median (range) actual number of cycles	Median (range) actual treatment duration (months)	Definition of relative dose intensity	Relative dose intensity	Median follow-up
Li 2023 (39) (China) (conference abstract)	NA/ 3,005/ 3,005	Median age (var): 60 (range: NR); n (%) male: NR; n (%) Asian: 3,005 (100)	Fruquintinib	NR	NR	NR	NR	Median RDI: 85.3%	NR

Abbreviations: NA, not applicable; NR, not reported; RDI, relative dose intensity; var, variance.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Bowel Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are the UK's leading bowel cancer charity. We are determined to save lives and improve the quality of life of everyone affected by bowel cancer by championing early diagnosis and access to best treatment and care. We support and fund targeted research, provide expert information and support to patients and their families, educate the public and professionals about the disease and campaign for early diagnosis and access to best treatment and care. The majority of our income is generated from individual, corporate and trust fundraisers. A small proportion is given by pharmaceutical and medical device companies in support of patient and healthcare professional education days and award-winning information sources.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information we provide in this response on the experiences of patients was gathered from a survey of people diagnosed with advanced bowel cancer who have undergone two systematic treatments. We posted a link to the survey via Google Forms on our patient online forum for two weeks and received responses anonymously.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A bowel cancer diagnosis is life-changing and can affect almost every aspect of daily life, not only for the individual diagnosed but also for their family and loved ones. This is even more acute for those diagnosed at the later stages of the disease, when it is harder to treat, and the chance of survival is lower. Patients experience numerous difficulties and challenges across the pathway, from getting an initial diagnosis to timely treatment and care. These challenges relate to the impact and reality of an advanced bowel cancer diagnosis, the difficulty and complexity in navigating treatment and care pathways and the impact treatment can have on quality of life. **Patients used words like 'traumatising', 'debilitating', 'overwhelming', and 'scary' to describe their overall experience living with advanced bowel cancer. Our community told us:** *"Debilitating. Chemo treatments affect quality of life greatly & in my case did not work."*

	"Repeat surgery due to chemo failing has left me dependent on medication to cope, not [to] be back to normal by any stretch, but [to] reduce the chance of unplanned defecation. My husband is distraught by it all." *"Absolutely traumatising."* *"Living with advanced bowel cancer is mentally and physically debilitating."* *"It's like a rollercoaster and the scariest ride that you can't get off. My dad has advanced bowel cancer and was given "short months" to live in June. He is still here. The mental and physical toll on all of us is overwhelming."* *"I have managed well physically and emotionally. My husband has found it harder to accept my prognosis."* **Patients undergoing treatments for advanced bowel cancer experience a range of side effects which significantly affect their quality of life – both physically and emotionally.** *"Folfox did not work & resulted in both making me very ill at the time. Delaying the doctors in scanning me & realising my cancer hadn't been eradicated by surgery & was growing rapidly. As well as leaving me with long term nerve damage in my hands & feet."* *"I struggle with rectal pain, and mentally can't even get out of bed some days."* *"Time is running out, [I] still have neuropathy."* *"I cannot return to work in my office, I cannot eat certain foods."* *"I am exhausted & nothing will be the same again."* *"There was a period 18 months ago when I was very tired and slept a lot but a small price to pay when you want to pursue any treatments available under the NHS. I lost all my hair but would do it again."* *"CAPOX, cold sensitivity, severe constipation, neuropathy. CAPIRI - severe constant fatigue, diarrhoea, stomach cramps"*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Survival for advanced bowel cancer is poor, with only 10.5% of people diagnosed surviving more than five years. These patients deserve access to the best quality treatment and care. For some patients these drugs can prolong life, so it is essential patients gain timely access to the treatments that their clinicians feel could benefit them. However, current treatment options approved for use on the NHS for advanced bowel cancer are extremely limited. The impact of this on patients' life expectancy and psychological wellbeing is detrimental, with many patients unable to access a treatment that could prolong their life and give them more time with their loved ones. This has financial implications for patients and their families, with many resorting to fundraising or borrowing money to fund treatments privately. This causes unnecessary stress, worry and anxiety when they are already struggling to come to terms with their diagnosis. **Our community told us:** *"It has for the most part been poor. I have struggled to get appointments. I have not been listened to. I have been talked down to by triage staff at hospital entrances hours away from my bowel rupturing as they didn't deem I was in as much pain as I said I was in."* *"I have been sent away time & again both over 3 years reporting issues & over 3 months with monthly re-admissions to hospital & disregarded as IBS/IBD/Ovary/Appendix & given the 'wait & see' 'treatment' until I became critical. I have been let down."* *"There is…a massive focus on the medical side rather than a balance with mental health and quality of life."* *"My dad has had 3 treatments of immunotherapy now. The staff in Hexham oncology day unit have been amazing!!! Dad is doing so well on the treatment and his tumour has started to shrink."* *"NHS care been amazing, very little contact with oncologist apart from 10 min apts every 3 months, cancer care wards so busy and the wait time for chair etc always added a few hours each visit but no fault of staff at all."* *"Had they given me immunotherapy first time round as research suggests is best for Lynch patients instead of chemo which made me very ill & didn't work then it would have been unlikely to have spread to my liver &*

	unlikely I would have had to have a hysterectomy In my 30s rendering me unable to have children & in menopause, dealing with those symptoms & health concerns."
8. Is there an unmet need for patients with this condition?	There is an unmet need for this specific patient population and all survey responders agreed. There are currently extremely limited treatment options available for people diagnosed with advanced bowel cancer. The evaluation of this technology is vital to increasing available treatments for advanced cancer patients receiving care on the NHS. **Our community told us:** *"Anyone who can have it and wants it should. THEIR LIVES ARE WORTH IT. Even if it only gives an extra 6 months, that's huge with a life expectancy of 2 years!"* *"I think if like myself they will try anything, they should have the option to try it, even on a 'trial' basis."* *"It should be available for those who want it, providing they feel fit enough to carry on with treatment."*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and carers support the provision of this technology on the NHS due to its potential to prolong life and improve treatment options. Many expressed frustrations at the lack of treatments available for stage 4 patients and believe that fruquintinib could offer greater hope to patients who have very few options for treatment. **Our community told us:** *"Everyone can benefit from this. A life is a life, and one is not more deserving than another! Anyone who can have it should have it."* *"All patients should be offered this."* *"We need to see Stage 4 as treatable, manageable, and curable."* *"Please give patients 'Options'."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	N/A

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	**Our community told us:** *"Everyone can benefit from this. A life is a life, and one is not more deserving than another! Anyone who can have it should have it."*

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/A

Other issues

13. Are there any other issues that you would like the committee to consider?	N/A

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A bowel cancer diagnosis can be life-changing for those diagnosed, as well as their friends and family, and is even more acute for those at later stages of the disease when it is harder to treat and there is a lower chance of survival. • Current treatment options approved for use on the NHS for advanced bowel cancer are extremely limited with many patients unable to access a treatment that could prolong their life. • Patients and carers advocated for access to fruquintinib to expand treatment options for advanced bowel cancer patients and increase progression-free survival. • Patients and carers stressed the impact of a lack treatment options and side effects from other treatments on their mental health during what is already a very difficult and distressing time, explaining that access to this treatment would offer more options, providing greater hope for prolonged survival.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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NICE National Institute for Health and Care Excellence

Part 1: Treating metastatic colorectal cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Harpreet Singh Wasan
2. Name of organisation	Imperial college healthcare NHS trust
3. Job title or position	Consultant and Professor Medical oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with metastatic colorectal cancer? ☒ A specialist in the clinical evidence base for metastatic colorectal cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for metastatic colorectal cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Improve Overall survival, slow progression with maintenance of quality of life as long as possible

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A hazard ratio for OS and PFS of <0.8 in 2 independent studies is the minimum threshold. An OS or PFS HR of <0.5 would be exceptional. And from a practical point of view for absolute values - an increase in OS of at least 2 months
10. In your view, is there an unmet need for patients and healthcare professionals in previously treated metastatic colorectal cancer?	Yes as current treatment sonly benefit a minority of patients treated <20%
11. How is previously treated metastatic colorectal cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	ESMO guidelines are the closest we have in UK although we do not have NHS funded access to Bevacizumab 1st or 2nd line or EGFR inhibitor monotherapy 3rd line - Generally, well defined for 1st and 2nd line with little variation across the UK Except academic centres may take a more aggressive multimodal approach as well as offer newer therapies in clinical trials - 3rd line+ less well defined / more variation as unclear if many DGH's have adequate patient support as patients approach later lines of therapy and there may be age (discrimination thresholds) and regional variation based on patient-support resource availability in ("overworked ') centres - No other 'level one' evidenced therapy available as fourth line with high efficacy in terms of OS/PFS HR's and well tolerated. Cross trial comparisons need to be treated with caution but the data for Fruquintinib (FRESCO 1 & 2 studies the latter a global phase 3, randomized, double-blind, placebo-controlled study) appears better than available 3rd line monotherapy options.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	There is very little use of fourth line therapies currently and hitherto no randomised trial post 3rd line treatment failure or intolerance Secondary and higher care especially if offered with monitoring and patients offered all other options including BSC and clinical trials.

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	No special facilities but education of new therapies implementation and profiles always advantageous and beneficial
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes significantly. Cross trial comparisons need to be treated with caution but the data for Fruquintinib (FRESCO 1 & 2 studies) appears better than available 3rd line monotherapy options. A hazard ratio for OS and PFS of 0.66 & 0.34 respectively andan increase in OS >2 months is clinically meaningful. Also impressive is that the benefit in RAS-mutant tumours and prior VEGF exposure still preserved efficacy. Health-related quality of life in 4th line mCRC is lacking any data before this trial. Fruquintinib was well tolerated in this heavily pre-treated patient population. The evidence from HRQOL data in the global phase 3, randomized, double-blind, placebo-controlled FRESCO-2 study was presented at ASCO GI last year and QLQ-C30 global health and EQ-5D-5L were not negatively impacted by treatment with Fruquintinib & numerically delayed time to deterioration in patient condition compared to placebo, which was consistent across most subscales
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not obviously. The data on prior Regorafenib use, is unclear as numbers are too small.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	As there is no approved 4th line regimen it has the same challenges as introduction of a new therapy in a condition where no available treatments are proven. Practically there will be traction for both patients and healthcare professionals as the efficacy data are very good and HRQOL is preserved and delivery is convenient as oral and scheduling 4 weekly. Patients not tolerating oral therapies may be disadvantaged eg severe uncontrolled nausea vomiting or dysphagia
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Standard rules of progression radiologically, intolerance or patient choice
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	QLQ-C30 global health and EQ-5D-5L are the best current tools we have and presented in the study. Oral delivery is convenient as oral and scheduling 4 weekly and better than IV
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes because the HR's suggest new level of efficacy in mCRC A step-change as the first truly 4th line 'unselected' study affecting all relevant population Survival in RAS mutants is poor so an unmet need improved by Fruquintinib

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As above Health-related quality of life in 4th line mCRC is lacking any data before this trial. Fruquintinib was well tolerated in this heavily pre-treated patient population. The evidence from HRQOL data in the global phase 3, randomized, double-blind, placebo-controlled FRESCO-2 study was presented at ASCO GI last year and QLQ-C30 global health and EQ-5D-5L were not negatively impacted by treatment with Fruquintinib & numerically delayed time to deterioration in patient condition compared to placebo, which was consistent across most subscales
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Broadly yes - as in UK although we do not have NHS funded access to Bevacizumab 1st or 2nd line or EGFR inhibitor monotherapy 3rd line which the study population reflected – the effect as a speculative judgement may be better in our population.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance regorafenib for previously treated metastatic colorectal cancer [TA866]?	i) The comparator is versus placebo and fourth line (which is novel) ii) The impact of possible NICE/ NICE adoption of third line Trifluridine-tipiracil + bevacizumab may need to be factored in for physician and patient choice as both add valuable contributions to the field and are not comparable as different populations (third versus 4th line)

23. How do data on real-world experience compare with the trial data?	This is embryonic so can't comment on this yet from UK experience There are non-UK studies which support & corroborate the FRESCO data efficacy safety and toxicity (Oncol Res. 2021; 29(1): 25–31. & 2) & some in abstract meeting formats (Journal of Clinical Oncology Volume 41, Number 16_suppl https://doi.org/10.1200/JCO.2023.41.16_suppl.e15557)
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Not obviously Less travel to hospital setting (compared to IV meds) may 'advantage" lower Socio-economic from less financial toxicity. I cannot envisage that the implementation would be contrary to any aspects of the Equality legislation.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is no other evidence- base for therapy available as fourth line treatment with high efficacy in mCRC in all subsets analysed including RAS- mutants and prior exposure to VEGF and EGFR inhibitors.
2 studies FRESCO 1 & 2, the latter a global phase 3, randomized, double-blind, placebo-controlled study
show consistent high benefit in overall and progression free survival
Fruquintinib is well tolerated and preserves health related quality of life

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Produced by Aberdeen HTA Group

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Moira Cruickshank reviewed and critiqued the clinical effectiveness evidence presented in the company submission; David Cooper checked and critiqued the statistical analyses presented in the company submission; Dwayne Boyers, Corinne Booth and Mary Kilonzo reviewed and critiqued the cost-effectiveness evidence and the economic model; Paul Manson checked and critiqued the company's search strategies; Michael Braun provided clinical guidance and comments on the draft report. Dwayne Boyers and Miriam Brazzelli coordinated all aspects of this appraisal and are the guarantors of this report. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

Abbreviation	Definition
ACJJ	American Joint Committee on Cancer
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criteria
AFT	Accelerated failure time
ASCO	American Society of Clinical Oncology
AUC	Area-under-the-curve
BIC	Bayesian information criteria
BNF	British National Formulary
BOR	Best overall response
BRAF	V-raf murine sarcoma viral oncogene homologue B
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CI	Confidence interval
CR	Complete response
CRC	Colorectal cancer
CrI	Credible interval
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
EAG	External assessment group
ECOG PS	Eastern Cooperative Oncology Group performance status
EEPRU	Economic Evaluation of Health and Care Interventions
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency

EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L	EuroQol five-dimension three-level
EQ-5D-5L	EuroQol five-dimension five-level
ESMO	European Society for Medical Oncology
FE	Fixed effects
FGFR	Fibroblast growth factor receptor
FOLFIRI	Folinic acid, fluorouracil and irinotecan
FOLFOX	Folinic acid, fluorouracil and oxaliplatin
FOLFOXIRI	Folinic acid, fluorouracil, oxaliplatin and irinotecan
G-CSF	Granulocyte colony-stimulating factor
GP	General practitioner
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KIT	KIT proto-oncogene receptor tyrosine kinase
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homologue
LSM	Least squares mean
LVEF	Left ventricular ejection fraction
MC	Monte Carlo
mCRC	Metastatic colorectal cancer
MMR	Mismatch repair
MOA	Mechanism of action
MRU	Medical resource use
MSI-H	Microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NHB	Net health benefit

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NTRK	Neurotrophic tyrosine receptor kinase
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD	Progressive disease
PD-1	Programmed cell death protein 1
PDGFR	Platelet-derived growth factor receptor-like protein
PFS	Progression-free survival
PH	Proportional hazards
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once a day
QLQ-C30	Core Quality of Life questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Proto-oncogene tyrosine-protein kinase receptor Ret
RWD	Real world data
RWE	Real world evidence
SD	Standard deviation
SLR	Systematic literature review

SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumour node metastasis
TTD	Time to treatment discontinuation
TTO	Time trade-off
UK	United Kingdom
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WTP	Willingness-to-pay
XELOX	Oxaliplatin and capecitabine

1. Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 describes a summary of the EAG's key issues. For this assessment, key issues identified by the EAG relate to differences of opinion between the company and EAG preferred base cases, rather than an EAG request for further consultation. Indeed, the EAG is satisfied that a detailed evidence submission has been provided by the company and further engagement would be unlikely to reduce uncertainty surrounding the most appropriate ICER for the committee.

Table 1 Summary of key issues

ID 6274	Summary of issue	Report sections
1	The EAG prefers the use of independently fitted OS and PFS curves for all treatments whereas the company prefers joint models from the pooled FRESCO and FRESCO-2 studies (fruquintinib and BSC) and HRs from the fixed-effects NMA for comparators (regorafenib and trifluridine-tipiracil).	4.2.6
2	The EAG prefers to model treatment acquisition costs for comparators (regorafenib and trifluridine-tipiracil) using median treatment duration and RDI from key clinical trials, whereas the company prefers to use the PFS HR and assume all RDIs are equal to those from the pooled FRESCO studies.	4.2.6 & 4.2.8

The key differences between the company and the EAG's preferred assumptions are outlined in Table 1 above. When compared to the company's base case economic model, the EAGs preferred OS and PFS assumptions (using trial data directly as opposed to estimates from the NMA) increase the QALY gains for fruquintinib compared to regorafenib and trifluridine-tipiracil, improving the cost-effectiveness case. However, the EAG prefers to fit independent curves to the pooled FRESCO study data, which reduces the incremental QALYs for fruquintinib compared to BSC, leading to a higher ICER. The EAGs preferred treatment acquisition cost assumptions (using median treatment time and relative dose intensities from the key clinical trials, as opposed to assumptions based on PFS HRs) reduce the treatment costs of comparators, increasing ICERs for fruquintinib. There are additional differences of opinion between the company and EAG about subsequent treatment costs and management costs of regorafenib, which do not have a major impact on the ICER but might be considered by the committee when deciding on a preferred set of base case assumptions.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival compared to other treatments and best supportive care (BSC)
- Increasing the time patients remain progression free, improving quality of life.
- An improved toxicity profile compared to regorafenib and trifluridine-tipiracil leading to a small QALY gain.

Overall, the technology is modelled to affect costs by:

- Leading to similar treatment acquisition costs to regorafenib (list price) but increasing treatment costs compared to trifluridine-tipiracil at list price and compared to BSC.
- Increasing disease management costs, due to longer time spent progression free.
- An improved toxicity profile compared to regorafenib and trifluridine-tipiracil leading to a small cost reduction.

The modelling assumptions that have the greatest effect on the ICER are:

- The size of the overall survival benefit which is determined by decisions around whether it is appropriate to apply HRs directly from the NMA.
- The duration and intensity of comparator treatments which has a substantial impact on treatment acquisition costs.

1.3 The decision problem: summary of the EAG's key issues

The main deviation from the NICE final scope is that the population was amended to align with the anticipated licensed indication. The company's approach is appropriate.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

In the company's submission, the primary evidence for the clinical effectiveness of fruquintinib for treating adults with previously treated metastatic colorectal cancer is based on the FRESCO and FRESCO-2 trials. To compare the effectiveness of fruquintinib with other relevant comparator treatments (placebo/BSC, trifluridine-tipiracil and regorafenib), the company presents fixed-effects NMAs. NMA results showed that fruquintinib was associated with a significant advantage in both OS and PFS vs BSC, a significant advantage in PFS vs

regorafenib and trifluridine-tipiracil, and a numerical advantage in OS vs regorafenib and trifluridine-tipiracil.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 1 OS and PFS extrapolation curve assumptions

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG prefers independently fitted OS and PFS curves for all treatments. The company prefers joint models from the FRESCO studies (fruquintinib and BSC) and HRs from the NMA (regorafenib and trifluridine-tipiracil). This issue has implications for the magnitude of QALY gains, and hence the ICER for fruquintinib versus the comparator treatments.
What alternative approach has the EAG suggested?	For comparisons of fruquintinib vs. BSC, it is unclear whether the proportional hazards assumption holds for the pooled FRESCO and FRESCO 2 study dataset, particularly for PFS. Independently fitted extrapolations give better fit to the observed KM data for BSC OS. The EAG are concerned that applying a HR directly to an accelerated failure time extrapolation curve (fruquintinib log-normal or generalised gamma) may over or underestimate OS and PFS at different points on the curve. The EAG's clinical expert considered the study populations across CORRECT, pooled FRESCO and FRESCO-2 studies, RECOURSE and Yoshino studies to be sufficiently comparable to allow a naïve comparison. The EAG prefers independently fitted curves, from the key clinical trials to fit OS and PFS curves for all comparators.
What is the expected effect on the cost-effectiveness estimates?	The EAGs assumptions increase QALY gains for fruquintinib compared to regorafenib and trifluridine-tipiracil, reducing the ICER. However, the incremental QALYs for fruquintinib compared to BSC are lower, leading to a higher ICER.
What additional evidence or analyses might help to resolve this key issue?	The EAG is satisfied that the company has provided sufficient evidence on which to make a decision regarding the most appropriate OS and PFS extrapolation assumptions.

Key: BSC, best supportive care; EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life years.

Issue 2 Regorafenib and trifluridine-tipiracil treatment discontinuation and relative dose intensity assumptions

Report section	4.2.6 & 4.2.8
Description of issue and why the EAG has identified it as important	The company calculated treatment acquisition costs for regorafenib and trifluridine-tipiracil by applying the PFS HRs to fruquintinib TTD curves. The company base case assumes all comparators have equal RDIs, set to the RDI from the pooled FRESCO and FRESCO-2 studies for fruquintinib. The EAG considers the company's approach to over-estimate comparator treatment acquisition costs.
What alternative approach has the EAG suggested?	The application of PFS HRs to TTD curves to estimate treatment discontinuation assumes that the hazards of treatment discontinuation follow a similar pattern to PFS, and that they are constant over time. This is unlikely to be the case because different treatments are likely to have different adverse event profiles, particularly regorafenib which may have higher initial treatment discontinuation rates than other comparators due to toxicity concerns. For relative dose intensity, the EAG's approach more accurately reflects the treatment specific RDI, is more aligned with clinical expectation of treatment dose adjustments for regorafenib and maintains consistency with the EAG's preferred data source for OS, PFS and ToT.
What is the expected effect on the cost-effectiveness estimates?	The EAGs preferred approach decreases the treatment acquisition costs for regorafenib and trifluridine-tipiracil, thereby increasing the ICER for Fruquintinib.
What additional evidence or analyses might help to resolve this key issue?	The EAG is satisfied that the company has provided sufficient evidence on which to make a decision regarding the most appropriate treatment discontinuation and relative dose intensity assumptions.

Key: EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PFS, progression free survival; RDI, relative dose intensity; TTD, time to treatment discontinuation; ToT, time on treatment

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 below reports the pairwise comparisons of fruquintinib vs. regorafenib, trifluridine-tipiracil and BSC, with a QALY severity weighting of 1.7 applied. The EAG is satisfied that a severity weighting of 1.7 is appropriate for the patient population for this assessment. One minor formula typographical error in the model and corrected by the EAG is described in Section 5.3. For further details of the exploratory and sensitivity analyses done by the EAG, see Chapter 6.

Table 2 Summary of EAG's preferred assumptions and ICER

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)
0. Company preferred base-case	[redacted]								
1. Independently fitted fruquintinib and BSC OS / PFS curves	[redacted]								
2. Independently fitted OS and PFS curves for regorafenib and trifluridine-tipiracil	[redacted]								
3. Scenarios 1 & 2 combined	[redacted]								
4. Fruquintinib TTD curve (Generalised gamma)	[redacted]								
5. Regorafenib and trifluridine-tipiracil TTD curves based on median time on treatment	[redacted]								
6. Scenarios 4 & 5 combined	[redacted]								
7. Trial specific RDIs applied to each comparator	[redacted]								
8. Apply eMIT prices for concomitant treatments	[redacted]								
9. Apply additional monitoring costs for regorafenib (2 x medical oncologist visits)	[redacted]								
10. Subsequent treatments based on company sought clinical expert opinion	[redacted]								
11. Duration of subsequent treatments (8 weeks)	[redacted]								
12. Scenarios 10 & 11 combined	[redacted]								

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)
13. EAG preferred base case analysis (Scenarios 3, 6, 7, 8, 9 & 12 combined)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Takeda is previously treated metastatic colorectal cancer. The company's description of this health condition in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is fruquintinib (Fruzaqla ®).

2.2 Background

The company's submission (CS) describes colorectal cancer (CRC) as a heterogeneous group of diseases involving the colon (around two-thirds of cases) or the rectum (around one-third of cases).[1-3] Most CRC evolves slowly from benign neoplasms (tubular adenomas and serrated polyps).[4] Some people have a genetic predisposition for polyps but most are found in people over the age of 50 and some go on to develop into CRC.[5-7] The majority of CRC are adenocarcinomas, arising in the cells that generate mucous for lubrication of the colon and rectum.[8] Early CRC can be asymptomatic, or with symptoms such as changes in bowel habits, rectal bleeding weight loss and anaemia.[9] Risk factors for CRC include personal or family history of CRC, personal history of colon polyps, inflammatory bowel disease, diabetes or cholecystectomy. Lifestyle considerations such as overweight/obesity, physical inactivity, smoking, alcohol intake and diet (eating processed meat and/or too little fibre can also be factors in the development of CRC.[10]

On average, there are 42,886 new cases of CRC each year in the UK, accounting for 11% of all cancer diagnoses.[11] Most patients in the UK with a new diagnosis of CRC are aged 85-89 years. In the year 2022-2023 in England, there were 100,163 admissions and 110,393 finished consultant episodes (FCE) for malignant neoplasm of the colon (code C18), and 49,879 admissions and 53,315 FCE for malignant neoplasm of the rectum (code C20).[12]

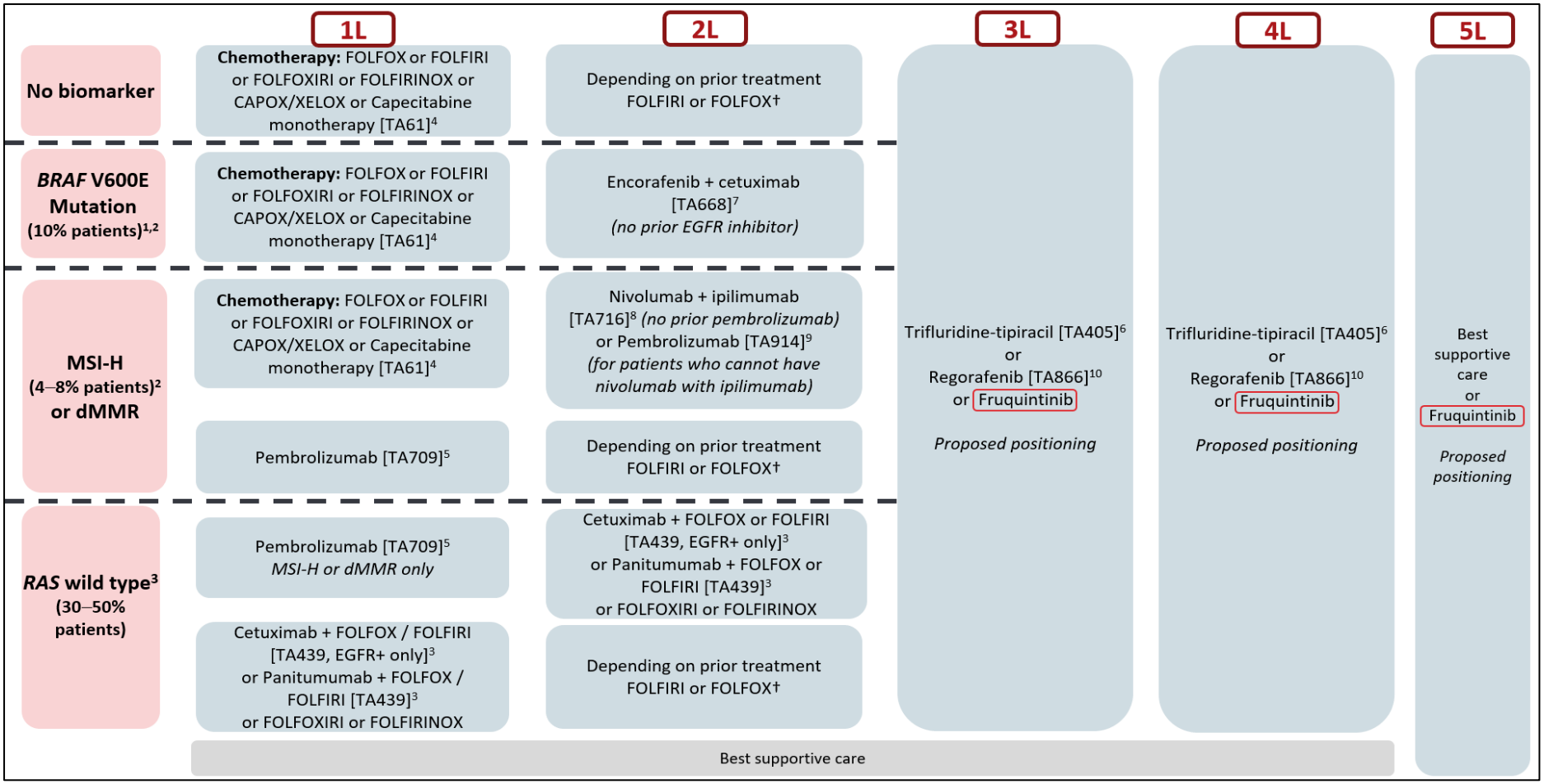
The earliest stage of CRC is referred to as stage 0 and stages I to IV refer to increasing spread of the disease, with stage IV referring to spread out with the colon or rectum, i.e. metastatic CRC (mCRC). Common sites of metastases in CRC include liver, lung, lymph nodes and peritoneum. Metastatic CRC is mainly incurable, with prognosis and treatment being related to the stage and biomarker profile of the disease, as well as the patient's overall fitness and co-morbidities. The aim of treatment is to improve or maintain quality of life and extend survival through control of the underlying CRC. Treatment can involve a number of

modalities, including radiotherapy, systemic therapy and surgery (which is less common). Best supportive care, a broad term covering a variety of approaches, may be the only option for many frail patients with significant co-morbidities, or those with such advanced disease that active treatment is inappropriate.[13-16]

The CS presents the currently available treatments for mCRC and the proposed positioning of fruquintinib as Figure 2, Document B of the CS, reproduced as Figure 1 below. The EAG's clinical expert agrees that the current standard of care in the 3rd-line and 4th-line settings is trifluridine-tipiracil or regorafenib. The EAG's clinical expert also considers the company's proposed positioning of fruquintinib at 3rd-, 4th- and 5th-line to be appropriate.

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 4.



Sources: Grothey et al, 2021,[17] Van Cutsem et al, 2016,[18] NICE TA709,[19] NICE TA439,[20] NICE TA716,[21] NICE TA668,[22] NICE TA61,[23] TA405,[24] NICE TA866,[25] NICE TA914.[26]
†Trifluridine-tipiracil may be given if 1L FOLFOXIRI or FOLFIRINOX and other 2L treatments are not suitable.
Abbreviations: 1L, first line; 2L, second line; 3L, third line; 4L, fourth line; 5L, fifth line; BRAF, v-raf murine sarcoma viral oncogene homologue B; CAPOX/XELOX, capecitabine and oxaliplatin; dMMR deficient mismatch repair; EGFR, epidermal growth factor receptor, MSI-H, microsatellite instability-high; FOLFIRINOX, fluorouracil, irinotecan and oxaliplatin; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; mCRC, metastatic colorectal cancer; NICE, National Institute for Health and Care Excellence; RAS, rat sarcoma virus; TA, technology assessment.

Figure 1 Proposed positioning of fruquintinib in the clinical pathway of care for mCRC [reproduced from Figure 2, Document B]

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with metastatic colorectal cancer (mCRC) who have had two or more previous treatments	The patient population is defined as [redacted]	The population is aligned with the anticipated licensed indication [27]	The EAG is satisfied with the company's approach
Intervention	Fruquintinib	As per final scope	–	The EAG is satisfied with the company's approach
Comparator(s)	• Trifluridine-tipiracil monotherapy • Regorafenib • Best supportive care	As per final scope	–	The EAG's clinical expert considers that the comparators addressed in the CS are appropriate
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates	As per final scope	–	The EAG's clinical expert is satisfied that the outcomes addressed in the CS are appropriate to the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Adverse effects of treatment • Health-related quality of life			
Economic analysis	The reference case specifies that the costs should be estimated from the NHS and PSS perspective and the health benefits should expressed as QALYs measured and valued using the EQ-5D. EQ-5D data should be reported directly by patients or their carers, and the source of the preference data for valuation should be representative sample of UK population. The economic evaluation should be conducted with fully incremental analysis. Costs and benefits should both be discounted at the same annual rate (3.5%) and that the time horizon should be long enough to reflect all important difference in costs and outcomes.	As per final scope	-	The EAG is satisfied that the economic analysis aligns closely with the NICE reference case. Results are reported as incremental cost per QALY gained using fully incremental and pairwise analyses (a severity weighting of 1.7 is applied throughout to incremental QALYs). The modelled time horizon of 10 years is sufficient to reflect a lifetime horizon for a patient group that have a high mortality risk at the end of the treatment pathway. The costing perspective is appropriate and confidential arrangements for the company's products are accounted for. Confidential arrangements for the comparators are provided in a confidential appendix to the EAG report.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Subgroups	The NICE final scope did not specify any subgroups.	-	-	The company performed subgroup analyses of OS and PFS for 14 subgroups in FRESCO and 23 subgroups in FRESCO-2. The EAG are satisfied this is a thorough sensitivity analysis and shows the treatment effects to be consistent. There are no notable subgroup differences to highlight. No subgroup analyses were presented for the economic analysis. The EAG are satisfied that this is appropriate.
Special considerations including issues related to equity or equality	No equity or equality issues relating to the use of fruquintinib were identified.	-	-	-

Key: mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; PSS, personal social services; QALY, Quality adjusted life years.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D and Section B.2.1, Document B of the CS. The EAG's critique of the methods used in the review is summarised in Table 4.

Table 4 EAG's appraisal of the systematic review methods presented in the CS.

Review process EAG	EAG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research. Relevant conference proceedings, trial registers and HTA organisations were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	Searches were not restricted by eligibility criteria, including limited by treatment line or metastatic terms, so all results were discovered and only those relevant to the scope were selected.
Was study selection conducted by two or more reviewers independently?	Yes	Two independent reviewers screened titles/abstracts and full text papers identified by the search strategies
Was data extraction conducted by two or more reviewers independently?	No	Data were extracted by one reviewer and validated by a second reviewer. The EAG considers this strategy to be acceptable
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	RCTs were assessed using the Cochrane risk of bias tool version 2. Other studies were assessed using the ROBINS-I tool

Review process EAG	EAG response	Comments
Was the risk of bias assessment conducted by two or more reviewers independently?	No	Risk of bias assessment was conducted by one reviewer and validated by a second reviewer. The EAG considers this strategy to be acceptable
Was identified evidence synthesised using appropriate methods?	Yes	The company have conducted meta-analyses and network meta-analyses where appropriate using methods recommended by NICE and consistent with earlier appraisals.

The EAG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 5. The EAG considers the methods used by the company for the systematic review of clinical effectiveness evidence to be appropriate.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are presented in Section B, Document B.2.3 of the CS. The main evidence for the clinical effectiveness and safety of fruquintinib consisted of two randomised, double blind, placebo controlled, multicentre, phase III trials: FRESCO and FRESCO-2.

The EAG has no major concerns about the design or conduct of these trials.

A further phase II RCT comparing fruquintinib with placebo in people with mCRC was identified in the company's systematic review.[28] The company did not present this trial as part of the clinical effectiveness evidence for this appraisal due to its phase II status but the trial was included in the subsequent network meta-analysis.

The EAG is satisfied with the company's approach.

The studies aimed to evaluate the efficacy and safety of fruquintinib in either patients with mCRC that had progressed after second-line or subsequent treatment (FRESCO) or patients with heavily pretreated mCRC (FRESCO-2). The primary endpoint in both studies was overall survival. An overview of the trials is reported in Table 5, Document B of the CS and reproduced as Table 6 below.

Table 6 Clinical effectiveness evidence for fruquintinib [reproduced from Table 5, Document B of the CS]

Study	**FRESCO (NCT02314819)**	**FRESCO-2 (NCT04322539)**
Study design	Randomised, double-blind, placebo-controlled, multicentre, Phase III study	Randomised, double-blind, placebo-controlled, multicentre, Phase III study
Population	Adult patients with mCRC who have failed two prior lines of treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, ± VEGF or EGFR inhibitors	Adult patients with refractory mCRC who have progressed on or been intolerant to treatment with chemotherapy, biological therapy and trifluridine-tipiracil and/or regorafenib
Intervention	Fruquintinib 5 mg PO, QD + BSC, 3 weeks on, 1 week off	Fruquintinib 5 mg PO, QD + BSC, 3 weeks on, 1 week off
Comparator	Placebo + BSC	Placebo + BSC
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes. In the economic model, clinical inputs for fruquintinib and BSC were informed by pooled data from FRESCO and FRESCO-2, including baseline characteristics, PFS, OS and TTD for fruquintinib and	

Study	FRESCO (NCT02314819)	FRESCO-2 (NCT04322539)
	PFS and OS for BSC, AE rates, RDI and subsequent therapies	
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	• OS • PFS • Response rates, including BOR, DCR and ORR • DOR • Adverse effects of treatments	• OS • PFS • Response rates, including BOR, DCR and ORR • DOR • Adverse effects of treatments • HRQoL
All other reported outcomes	N/A	N/A
Sources of evidence	Published data sources: • Li et al, 2018 (primary manuscript)[29] • Secondary data sources[30-33] • Unpublished data source: • CSR[32]	• Published data sources: • Dasari et al, 2023 (primary manuscript)[34] • Secondary data sources[18, 35-40] • Unpublished data source: • CSR[39]

Key: AE, adverse event; BOR, best overall response; BSC, best supportive care; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; mCRC, metastatic colorectal cancer; N/A, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; QD, once daily; QLQ-C30, Core Quality of Life questionnaire; RDI, relative dose intensity; TTD, time to treatment discontinuation; VEGF, vascular endothelial growth factor.

FRESCO was conducted in 28 centres in China and FRESCO-2 in 124 centres in Australia, Europe, Japan and USA. Three centres in the UK enrolled a total of three patients. Key inclusion and exclusion criteria for FRESCO and FRESCO-2 are reported in Table 6, Document B of the CS. In brief, both trials recruited adults with mCRC who had received at least two prior lines of systemic therapy. Both trials randomised patients 2:1 to receive either fruquintinib 5mg or placebo orally, once daily for 21 days, followed by 7 days off in 28-day cycles until disease progression, intolerable toxicity or withdrawal from study. Both treatment arms also received best supportive care (BSC), defined as any treatment necessary for health and not

anticipated to interfere with study drug and was determined locally by the investigator.

Patient disposition in the trials is reported in Figures 47 and 48, Appendix D of the CS. In FRESCO, 278 patients were randomised to receive fruquintinib and 138 were randomised to receive placebo. At the end of the treatment period, 24 (8.6%) and 1 patient (0.7%), respectively, were still receiving treatment. In FRESCO-2, 461 and 230 patients were randomised to receive fruquintinib or placebo, respectively, with 20 (4.3%) and 1 (0.4%), respectively, still receiving treatment at the end of the treatment period.

The company performed quality appraisals on FRESCO and FRESCO-2 using Version 2 of the Cochrane Risk of Bias tool.[41] *The EAG agrees with the company's assessments and that both trials are at low risk of bias*.

The company's economic model was informed by pooled data from the FRESCO and FRESCO-2 trials. Thus, baseline demographics/disease characteristics and OS/PFS outcomes will be reported for each of the trials individually and for the pooled data. Details of the baseline demographic and disease characteristics of FRESCO and FRESCO-2 are reported in Table 7, Document B of the CS, and pooled FRESCO and FRESCO-2 data are reported in Table 14, Document B of the CS. These are adapted as Table 7 below. *In general, characteristics were similar between groups in both trials.*

The company acknowledges that there are differences between the trials in terms of participants' ethnicity (FRESCO was conducted in a Chinese only population; FRESCO-2 in Australia, Europe, Japan and USA) and proportion of participants with prior use of VEGF inhibitors (FRESCO, 30.2%; FRESCO-2, 95.5%).

The EAG's clinical expert agrees with the company that ethnicity is not a treatment modifier in this clinical population, but that prior anti-VEGF therapy probably would affect effectiveness of treatment. For those reasons, the EAG's clinical expert is of the opinion that the population of FRESCO is more aligned to patients seen in UK clinical practice than the FRESCO-2 population.

In addition, the EAG noted that the mean age of participants in FRESCO (54.3 in the fruquintinib group, 55.1 in the placebo group) and FRESCO-2 (62.2 and 62,4, respectively) was younger than would be seen in UK clinical practice. Furthermore, UK patients with an ECOG score of zero would be unusual. Furthermore, the EAG's clinical expert noted that FRESCO2 had more patients who were PS0 than the FRESCO study. The FRESCO study participants were therefore probably more reflective of "real world" clinical practice.

Participants in FRESCO-2 also had longer-standing metastatic disease (mean 44.01 and 46.54 months versus 18.92 and 20.57 months, respectively) and were more heavily pre-treated (median 5 treatment lines in both groups versus 3 lines in both groups) than participants in FRESCO. Thus, the EAG's clinical expert considers that participants in FRESCO-2 may be less likely than those in FRESCO to benefit from treatment.

Table 7 Summary of baseline demographics and disease characteristics – FRESCO and FRESCO-2, ITT population, and the two studies pooled [adapted from Tables 7 and 14, Document B of the CS]

Category	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Fruquintinib + BSC N=739	Placebo + BSC N=368
Age, years						
Mean (SD)	54.3 (10.70)	55.1 (10.53)	62.2 (10.41)	62.4 (9.67)	59.2 (11.17)	59.7 (10.60)
Sex, n (%)						
Female	120 (43.2)	41 (29.7)	216 (46.9)	90 (39.1)	336 (45.5)	131 (35.6)
Male	158 (56.8)	97 (70.3)	245 (53.1)	140 (60.9)	403 (54.5)	237 (64.4)
Race, n (%)						
American Indian or Alaska native	0	0	0	1 (0.4)	0	1 (0.3)
Asian	278 (100)	138 (100)	43 (9.3)	18 (7.8)	321 (43.4)	156 (42.4)
Black or African American	0	0	13 (2.8)	7 (3.0)	13 (1.8)	7 (1.9)
Native Hawaiian or other Pacific Islander	0	0	3 (0.7)	2 (0.9)	3 (0.4)	2 (0.5)
White	0	0	367 (79.6)	192 (83.5)	367 (49.7)	192 (52.2)
Other	0	0	5 (1.1)	2 (0.9)	5 (0.7)	2 (0.5)
Multiple races	0	0	2 (0.4)	0	2 (0.3)	0
Not reported/unknown	0	0	28 (6.1)	8 (3.5)	28 (3.8)	8 (2.2)
Ethnicity, n (%)						
Han Chinese	272 (97.8)	135 (97.8)	0	0	272 (36.8)	135 (36.7)

Category	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Fruquintinib + BSC N=739	Placebo + BSC N=368
Non-Han Chinese	6 (2.2)	3 (2.2)	0	0	6 (0.8)	3 (0.8)
Hispanic or Latino	0	0	20 (4.3)	14 (6.1)	20 (2.7)	14 (3.8)
Not Hispanic or Latino	0	0	405 (87.9)	202 (87.8)	405 (54.8)	202 (54.9)
Not reported/unknown	0	0	36 (7.8)	14 (6.1)	36 (4.9)	14 (3.8)
Region and Country, n (%)						
China	278 (100)	138 (100)	0	0	278 (37.6)	138 (37.5)
North America	0	0	82 (17.8)	42 (18.3)	82 (11.1)	42 (11.4)
Europe	0	0	329 (71.4)	166 (72.2)	329 (44.5)	166 (45.1)
Asia Pacific (Japan and Australia)	0	0	50 (10.8)	22 (9.6)	50 (6.7)	22 (6.0)
BMI (kg/m^2)						
n	278	138	450	225	728	363
Mean (SD)	23.19 (3.286)	23.52 (3.429)	26.00 (5.159)	25.77 (5.218)	24.93 (4.74)	24.91 (4.74)
ECOG PS, n (%)						
0	77 (27.7)	37 (26.8)	196 (42.5)	102 (44.3)	273 (36.9)	139 (37.8)
1	201 (72.3)	101 (73.2)	265 (57.5)	128 (55.7)	466 (63.1)	229 (62.2)
Time since first diagnosis of CRC (months)						
n	277[†]	138	461	230	NR	NR
Mean (SD)	2.24 (1.548)	2.43 (1.788)	52.74 (30.406)	56.02 (28.846)	NR	NR
Median	1.79	2.04	47.18	49.38	NR	NR

Category	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Fruquintinib + BSC N=739	Placebo + BSC N=368
Min, max	0.1, 9.7	0.3, 9.8	6.0, 242.4	7.1, 154.4	NR	NR
Stage of CRC at first diagnosis, n (%)						
Stage I	8 (2.9)	4 (2.9)	20 (4.3)	6 (2.6)	28 (3.8)	10 (2.7)
Stage II	34 (12.2)	18 (13.0)	32 (6.9)	17 (7.4)	66 (8.9)	35 (9.5)
Stage III	118 (42.4)	51 (37.0)	139 (30.2)	84 (36.5)	257 (34.8)	135 (36.7)
Stage IV	117 (42.1)	63 (45.7)	264 (57.3)	119 (51.7)	381 (51.6)	182 (49.5)
Missing	1 (0.4)	2 (1.4)	6 (1.3)	4 (1.7)	7 (0.9)	6 (1.6)
Primary site at first diagnosis, n (%)						
Colon	147 (52.9)	70 (50.7)	279 (60.5)	137 (59.6)	426 (57.6)	207 (56.3)
Rectum	125 (45.0)	60 (43.5)	143 (31.0)	70 (30.4)	268 (36.3)	130 (35.3)
Colon-rectum	6 (2.2)	7 (5.1)	39 (8.5)	23 (10.0)	45 (6.1)	30 (8.2)
Missing	0	1 (0.7)	0	0	0	1 (0.2)
Primary tumour location at first diagnosis, n (%)						
Left (splenic flexure, descending/transverse /sigmoid colon and rectum)	214 (77.0)	115 (83.3)	335 (72.7)	162 (70.4)	549 (74.3)	277 (75.3)
Right (caecum, ascending colon and hepatic flexure)	56 (20.1)	21 (15.2)	97 (21.0)	53 (23.0)	153 (20.7)	74 (20.1)
Left and right	4 (1.4)	0	4 (0.9)	2 (0.9)	8 (1.1)	2 (0.5)
Unknown	4 (1.4)	1 (0.7)	25 (5.4)	13 (5.7)	29 (3.9)	14 (3.8)
Missing	0	1 (0.7)	0	0	0	1 (0.3)

Category	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Fruquintinib + BSC N=739	Placebo + BSC N=368
Duration of metastatic disease (months)						
n	278	138	461	230	NR	NR
Mean (SD)	18.92 (12.946)	20.57 (14.626)	44.01 (23.978)	46.65 (24.607)	NR	NR
Median	16.03	17.22	37.88	40.97	NR	NR
Min, max	0.9, 79.0	1.9, 81.6	6.0, 192.8	7.1, 147.1	NR	NR
Categories, n (%)					NR	NR
<18 months[‡]/≤18 months[§]	163 (58.6)	75 (54.3)	37 (8.0)	13 (5.7)	NR	NR
≥18 months[‡]/>18 months[§]	115 (41.4)	63 (45.7)	424 (92.0)	217 (94.3)	NR	NR
Liver metastases, n (%)						
Yes	185 (66.5)	102 (73.9)	339 (73.5)	156 (67.8)	524 (70.9)	258 (70.1)
No	93 (33.5)	36 (26.1)	122 (26.5)	74 (32.2)	215 (29.1)	110 (29.9)
***KRAS*[‡]/*RAS*[§] gene status, n (%)**						
Wild type	157 (56.5)	74 (53.6)	170 (36.9)	85 (37.0)	327 (44.2)	159 (43.2)
Mutant	121 (43.5)	64 (46.4)	291 (63.1)	145 (63.0)	412 (55.8)	209 (56.8)
***BRAF*[§] gene status, n (%)**						
Wild type	NR	NR	401 (87.0)	198 (86.1)	NR	NR
V600E mutation	NR	NR	7 (1.5)	10 (4.3)	NR	NR
Other mutation	NR	NR	53 (11.5)	22 (9.6)	NR	NR
Microsatellite/Mismatch repair status, n (%)						
MSS and/or pMMR	NR	NR	427 (92.6)	215 (93.5)	NR	NR

Category	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Fruquintinib + BSC N=739	Placebo + BSC N=368
MSI-H and/or dMMR	NR	NR	5 (1.1)	4 (1.7)	NR	NR
Unknown	NR	NR	29 (6.3)	11 (4.8)	NR	NR
Prior use of VEGF inhibitor, n (%)						
Yes	84 (30.2)	41 (29.7)	445 (96.5)	221 (96.1)	529 (71.6)	226 (71.2)
No	194 (69.8)	97 (70.3)	16 (3.5)	9 (3.9)	210 (28.4)	106 (28.8)
Prior use of EGFR inhibitor, n (%)						
Yes	40 (14.4)	19 (13.8)	180 (39.0)	88 (38.3)	220 (29.8)	107 (29.1)
No	238 (85.6)	119 (86.2)	281 (61.0)	142 (61.7)	519 (70.2)	261 (70.9)
Prior treatment with EGFR/VEGF inhibitors, n (%)						
No anti-VEGF and no anti-EGFR	167 (60.1)	83 (60.1)	4 (0.9)	5 (2.2)	171 (23.1)	88 (23.9)
Anti-VEGF, anti-EGFR or both	111 (39.9)	55 (39.9)	457 (99.1)	225 (97.8)	568 (76.9)	280 (76.1)
Anti-VEGF and no anti-EGFR	71 (25.5)	36 (26.1)	277 (60.1)	137 (59.6)	348 (47.1)	173 (47.0)
Anti-EGFR and no anti-VEGF	27 (9.7)	14 (10.1)	12 (2.6)	4 (1.7)	39 (5.3)	18 (4.9)
Both anti-VEGF and anti-EGFR	13 (4.7)	5 (3.6)	168 (36.4)	84 (36.5)	181 (24.5)	89 (24.2)
Prior treatment with trifluridine-tipiracil and/or regorafenib, n (%)[§]						
Trifluridine-tipiracil	0	0	240 (52.1)	121 (52.6)	240 (32.5)	121 (32.9)

Category	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Fruquintinib + BSC N=739	Placebo + BSC N=368
Regorafenib	0	0	40 (8.7)	18 (7.8)	40 (5.4)	18 (4.9)
Trifluridine-tipiracil and regorafenib	0	0	181 (39.3)	91 (39.6)	181 (24.5)	91 (24.7)
Number of prior treatment lines						
Median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	NR	NR
2 or 3, n (%)	190 (68.3)	98 (71.0)	77 (16.7)	44 (19.1)	267 (36.1)	142 (38.6)
>3, n (%)	88 (31.7)	40 (29.0)	384 (83.3)	186 (80.9)	472 (63.9)	226 (61.4)
Number of prior treatment lines for metastatic disease, n (%)						
≤3	221 (79.5)	107 (77.5)	125 (27.1)	64 (27.8)	346 (46.8)	171 (46.4)
>3	57 (20.5)	31 (22.5)	336 (72.9)	166 (72.2)	393 (53.2)	197 (53.5)

Source: FRESCO final CSR,[32] FRESCO tables,[32] FRESCO-2 final CSR,[39] Dasari et al, 2023.[42]
†Time of first diagnosis was missing for one patient; ‡FRESCO only; §FRESCO-2 only.
Key: BMI, body mass index; BRAF, v-raf murine sarcoma viral oncogene homologue B; BSC, best supportive care; CSR, clinical study report; CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor; ITT, intention-to-treat; KRAS, Kirsten rat sarcoma viral oncogene homologue; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NR, not reported; pMMR, proficient mismatch repair; Q, quartile; RAS, rat sarcoma virus; SD, standard deviation; VEGF, vascular endothelial growth factor

3.2.2 Primary and secondary efficacy endpoints

Efficacy analyses were conducted on the intention-to-treat (ITT) set of both trials, which consisted of all randomised patients.

Primary endpoint

- **Overall survival** (OS; defined as time from randomisation until death): Table 8 reports a summary of OS from the FRESCO and FRESCO-2 trials and pooled data from the two trials. The company presents Kaplan-Meier curves for OS for FRESCO (Figure 5), FRESCO-2 (Figure 6) and pooled FRESCO and FRESCO-2 (Figure 13) in Document B of the CS. Median duration of treatment in FRESCO was 3.7 months and 1.8 months in the fruquintinib and placebo groups, respectively, and 3.1 months and 1.8 months, respectively, in FRESCO-2. In FRESCO, 188 patients in the fruquintinib group (67.6%) and 109 patients in the placebo group (79.0%) died. In FRESCO-2, there were 317 deaths (68.8%) and 173 deaths (75.2%), respectively. The pooled analysis showed that a total of 68.3% of the fruquintinib group died as compared to 76.6% of the placebo group. Median OS in the fruquintinib and placebo groups in FRESCO was 9.3 months and 6.6 months, respectively, HR 0.65 (95%CI 0.51, 0.83; p<0.001). In FRESCO-2, median OS in the two groups was 7.4 months and 4.8 months, respectively, HR 0.66 (SE 0.10; p<0.001). Median OS in the pooled analysis was 8.0 months and 5.6 months, respectively, HR 0.67 (SE 0.08; p<0.0001).

Table 8 Summary of OS – FRESCO, FRESCO-2 and pooled data from the two trials [adapted from Table 11, Document B and Table 1, Appendix N of the CS]

	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=138**	**Fruquintinib + BSC N=461**	**Placebo + BSC N=230**	**Fruquintinib + BSC N=739**	**Placebo + BSC N=368**
No. of patients who died, n (%)	188 (67.6)	109 (79.0)	317 (68.8)	173 (75.2)	505 (68.3)	282 (76.6)
No. of patients censored, n (%)	90 (32.4)	29 (21.0)	144 (31.2)	57 (24.8)	234 (31.7)	86 (23.4)
Censoring reasons, n (%)						
Alive	83 (29.9)	24 (17.4)	127 (27.5)	49 (21.3)	210 (89.7)	73 (84.9)
Lost to follow-up	3 (1.1)	1 (0.7)	3 (0.7)	0	6 (2.6)	1 (1.2)
Withdrawal of consent	4 (1.4)	4 (2.9)	14 (3.0)	8 (3.5)	18 (7.7)	2 (14)
OS (months)						
Median (95%CI)	9.30 (8.18, 10.45)	6.57 (5.88, 8.11)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)	8.02 (7.43, 8.74)	5.55 (4.80, 6.24)
Probability (%) of being alive at: (95% CI)						
3 months	90.6 (87.1, 94.0)	80.8 (74.1, 87.4)	88.1 (85.1, 91.1)	68.8 (62.8, 74.9)	89.0 (86.8, 91.3)	73.3 (68.8, 77.9)
6 months	69.5 (64.0, 74.9)	54.1 (45.7, 62.5)	60.4 (55.9, 64.9)	41.5 (35.0, 48.0)	63.8 (60.3, 67.4)	46.2 (41.1, 51.4)
9 months	51.3 (45.4, 57.3)	34.7 (26.5, 42.9)	41.1 (36.4, 45.8)	28.2 (22.1, 34.3)	45.0 (41.4, 48.7)	30.6 (25.7, 35.5)

	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=138**	**Fruquintinib + BSC N=461**	**Placebo + BSC N=230**	**Fruquintinib + BSC N=739**	**Placebo + BSC N=368**
12 months	34.3 (28.1, 40.4)	18.0 (10.5, 25.4)	27.8 (23.0, 32.6)	23.2 (17.1, 29.2)	30.2 (26.5, 34.0)	20.9 (16.1, 25.6)
18 months	18.3 (11.8, 24.9)	9.0 (2.1, 15.9)	8.3 (2.3, 14.2)	10.3 (3.9, 16.8)	13.2 (9.0, 17.4)	8.9 (3.8, 14.1)
Duration (months) of follow-up						
Median (95% CI)	13.31 (–)	13.24 (–)	11.3 (10.6, 12.4)	11.2 (9.9, 12.0)	12.09 (11.63, 12.78)	11.40 (10.78, 13.04)
Comparison (fruquintinib vs placebo)						
Stratified HR (95%CI)†/(SE)‡	0.65 (0.51, 0.83)		0.66 (0.10)		0.660 (0.075)	
95% CI‡	–		(0.55, 0.80)		(0.570, 0.764)	
p-value of stratified log-rank test†/two-sided p-value‡	<0.001		<0.001		<0.0001	

Source: FRESCO final CSR,[32] FRESCO-2 final CSR.[39]
†FRESCO only; ‡FRESCO-2 only.
Key: BSC, best supportive care; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; SE, standard error.

Secondary endpoints

- **Progression-free survival** (PFS; defined as time from randomisation to disease progression or death, whichever occurs first): By the end of follow-up, 235 patients in the fruquintinib group (84.5%) and 125 patients in the placebo group (90.6%) of FRESCO had experienced PD or death. In FRESCO-2, 392 patients (85.0%) and 213 patients (92.6%), respectively, had experienced these outcomes. Median PFS was longer in the fruquintinib group (3.7 months) than the placebo group (1.8 months) in both FRESCO (HR 0.26, 95%CI 0.21-0.34; p<0.001) and FRESCO-2 (HR 0.32, 95%CI 0.27-0.39; p<0.001). In the pooled analysis of FRESCO and FRESCO-2, a total of 84.8% of fruquintinib participants and 91.8% of placebo participants experienced PD or death. Median PFS was 3.7 months and 1.8 months, respectively, HR 0.31 (95%CI 0.27, 0.36). Kaplan Meier curves for PFS in FRESCO and FRESCO-2 are presented in Figures 7 and 8, respectively, of Document B of the CS and Figure 14 presents the PFS pooled analysis.
- **Response rates:** The following are reported in Table 13, Document B (FRESCO and FRESCO-2 individually) and Table 3, Appendix N of the CS, adapted as Table 9 below.
    - Best overall response (BOR; defined as the best efficacy recorded from randomisation to objectively recorded progression as per RECIST v1.1 or the start of subsequent anti-cancer treatment, whichever occurred first)
    - Objective response rate (ORR; defined as the percentage of patients with BOR of complete response [CR] or partial response [PR] compared to baseline)
    - Disease control rate (DCR; defined as the percentage of patients with BOR of CR, PR or stable disease [SD])
    - Duration of response (DOR; defined as the time from first objective CR or PR to time of occurrence of PD or death)

Table 9 Summary of BOR, ORR and DCR – FRESCO and FRESCO-2, ITT population [adapted from Table 13, Document B and Table 3, Appendix N of the CS]

	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Fruquintinib + BSC N=739	Placebo + BSC N=368
BOR, n (%)						
CR	1 (0.4)	0	0	0	1 (0.1)	0
PR	12 (4.3)	0	7 (1.5)	0	19 (2.6)	0
Stable disease	160 (57.6)	17 (12.3)	249 (54.0)	37 (16.1)	409 (55.3)	54 (14.7)
CR – unconfirmed	–	–	0	0	NR	NR
PR – unconfirmed	–	–	5 (1.1)	0	NR	NR
PD	87 (31.3)	98 (71.0)	139 (30.2)	143 (62.2)	226 (30.6)	241 (65.5)
NE	18 (6.5)	23 (16.7)	6 (1.3)	1 (0.4)	24 (3.2)	24 (6.5)
NA	–	–	60 (13.0)	49 (21.3)	60 (8.1)	49 (13.3)
ORR: CR + PR, n (%)	13 (4.7)	0	7 (1.5)	0	20 (2.7)	0
Exact 95% CI[†]/two-sided 95% CI[‡]	2.51, 7.86	0.00, 2.64	0.6, 3.1	0.0, 1.6	1.7, 4.1	0.0, 1.0
Odds ratio (95%CI)[†]	– (1.997, –)		–		NR	NR
Adjusted difference (fruquintinib – placebo) (SE)[‡]	–		1.5 (0.006)		2.7 (0.0006)	-
95% CI[‡]	–		0.4, 2.7		1.5, 3.9	-
Two-sided p-value[†]/p-value of exact test[‡]	0.012		0.059		0.0014	-

	FRESCO		FRESCO-2		Pooled FRESCO and FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=138**	**Fruquintinib + BSC N=461**	**Placebo + BSC N=230**	**Fruquintinib + BSC N=739**	**Placebo + BSC N=368**
DCR: CR + PR + stable disease for at least 7 weeks, n (%)	173 (62.2)	17 (12.3)	256 (55.5)	37 (16.1)	429 (58.1)	54 (14.7)
Exact 95%CI†/two-sided95% CI‡	56.25, 67.95	7.34, 18.99	50.9, 60.1	11.6, 21.5	54.4, 61.6	11.2, 18.7
Odds ratio (95%CI)†					NR	NR
Adjusted difference (fruquintinib – placebo) (SE)‡	–		39.4 (0.034)		43.4 (0.026)	-
95% CI‡	–		32.8, 46.0		38.3, 48.4	-
Two-sided p-value†/p-value of CMH test‡	<0.001		<0.001		<0.0001	-
DOR, months						
25th percentile (95% CI)	–	–	10.7 (3.9, NE)	–	NR	NR
Median (95% CI)	–	–	10.7 (3.9, NE)	–	NR	NR
75th percentile (95% CI)	–	–	NE (10.7, NE)	–	NR	NR
Min, max	–	–	2.1, 16.9	–	NR	NR

Source: FRESCO final CSR,[32] FRESCO-2 final CSR,[39] FRESCO and FRESCO-2 pooled data.
†FRESCO only; ‡FRESCO-2 only.
Key: BOR, best overall response; BSC, best supportive care; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CR, complete response; CSR, clinical study report; DCR, disease control rate; DOR, duration of response; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PR, partial response; SE, standard error.

- **Health-related quality of life** (HRQoL): Assessed in FRESCO-2 only using the EORTC QLQ-C30 and EuroQol EQ-5D-5L questionnaires. HRQoL results are reported in Section B.2.6.2.3, Document B of the CS. The company reported that change from baseline scores on both instruments indicated a slower worsening of clinical condition and a delay in the risk of deterioration in the fruquintinib group as compared to the placebo group. The EAG agrees with this statement up to cycle 3. However, there appears to be a switch between cycles 3 and 4, with the QLQ-C30 improving considerably and the EQ-5D improving slightly in the placebo group but no improvement on the QLQ-30 and deterioration in the EQ-5D in the fruquintinib group (Figure 9 and 10, Document B of the CS). At clarification, the company explained that the Cycle 4 results were influenced by the decreasing numbers of participants over time. The EAG is satisfied with the company's explanation.

3.2.3 Subgroup analyses

To assess the homogeneity of treatment effect across patient subgroups, the company performed subgroup analyses of OS and PFS for specified subgroups (14 subgroup analyses in FRESCO and 23 analyses in FRESCO-2) [reported in Section B.2.7, Document B and Appendix E of the CS]. For most subgroups, hazard ratios were in favour of fruquintinib over placebo and the EAG agrees that the subgroup analyses demonstrate superiority of fruquintinib over placebo for most subgroups.

3.2.4 Adverse events

The safety sets in FRESCO and FRESCO-2 were defined as all patients in the ITT sets who received at least one dose of the study drug. In FRESCO, median treatment exposure was 3.7 months in the fruquintinib group and 1.8 months in the placebo group and, in FRESCO-2, 3.1 months and 1.8 months, respectively.

An overall summary of TEAEs in FRESCO and FRESCO-2 is reported by the company in Table 23, Document B of the CS and reproduced as Table 10 below (and subsequently updated following the company's response at the FAC).

Table 10 Overall summary of TEAEs – FRESCO and FRESCO-2, safety sets [reproduced from Table 23, Document B of the CS and updated from Clarification Table 10 of the FAC document]

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=137**	**Fruquintinib + BSC N=456**	**Placebo + BSC N=230**
Patients with any TEAE, n (%)	**274 (98.6)**	**121 (88.3)**	**451 (98.9)**	**213 (92.6)**
CTCAE Grade ≥3	170 (61.2)	27 (19.7)	286 (62.7)	116 (50.4)
Treatment-related	266 (95.7)	97 (70.8)	395 (86.6)	130 (56.5)
Treatment-related CTCAE Grade ≥3	128 (46.0)	10 (7.3)	164 (36.0)	26 (11.3)
Leading to dose reduction	67 (24.1)	6 (4.4)	110 (24.1)	9 (3.9)
Leading to dose interruption	98 (35.3)	14 (10.2)	213 (46.7)	61 (26.5)
Leading to treatment discontinuation	42 (15.1)	8 (5.8)	93 (20.4)	49 (21.3)
Treatment-related leading to dose reduction	61 (21.9)	3 (2.2)	93 (20.4)	7 (3.0)
Treatment-related leading to dose interruption	87 (31.3)	10 (7.3)	134 (29.4)	14 (6.1)
Treatment-related leading to treatment discontinuation	22 (7.9)	1 (0.7)	45 (9.9)	7 (3.0)
TEAE leading to death	9 (3.2)	2 (1.5)	49 (10.7)	45 (19.6)
Treatment-related TEAE leading to death	4 (1.4)	0	1 (0.4)	1 (0.5)
Patients with any serious TEAE, n (%)	**43 (15.5)**	**8 (5.8)**	**172 (37.7)**	**88 (38.3)**
CTCAE Grade ≥3	32 (11.5)	7 (5.1)	163 (35.7)	85 (37.0)
Treatment-related	17 (6.1)	2 (1.5)	43 (9.4)	8 (3.5)
Treatment-related CTCAE Grade ≥3	128 (46.0)	10 (7.3)	38 (8.3)	6 (2.6)
Patients with any AESI, n (%)	**257 (92.4)**	**74 (54.0)**	**368 (80.7)**	**122 (53.0)**
Patients with any COVID-19-related TEAEs, n (%)	**N/A**	**N/A**	**14 (3.1)**	**8 (3.5)**
CTCAE Grade ≥3	N/A	N/A	1 (0.2)	5 (2.2)
Serious	N/A	N/A	1 (0.2)	5 (2.2)
Treatment-related	N/A	N/A	0	0
Treatment-related CTCAE Grade ≥3	N/A	N/A	0	0
Leading to dose reduction	N/A	N/A	0	0

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=137**	**Fruquintinib + BSC N=456**	**Placebo + BSC N=230**
Leading to dose interruption	N/A	N/A	6 (1.3)	4 (1.7)
Leading to treatment discontinuation	N/A	N/A	0	1 (0.4)
Treatment-related leading to dose reduction	N/A	N/A	0	0
Treatment-related leading to dose interruption	N/A	N/A	0	0
Treatment-related leading to treatment discontinuation	N/A	N/A	0	0
Leading to death	N/A	N/A	0	1 (0.4)

Source: FRESCO final CSR,[32] FRESCO-2 final CSR.[39]
Key: AESI, adverse event of special interest; BSC, best supportive care; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; N/A, not applicable; TEAE, treatment-emergent adverse event.

Almost all participants in the fruquintinib groups of FRESCO (98.6%) and FRESCO-2 (98.9%) experienced at least one TEAE, with slightly lower proportions in the placebo groups (88.3% and 92.6%, respectively).

Serious TEAEs were experienced by a greater proportion of participants in the fruquintinib group (15.5%) than the placebo group (5.8%) in FRESCO but in similar proportions of the fruquintinib (37.7%) and placebo (38.3%) groups in FRESCO-2. Treatment-related TEAEs of Grade ≥3 were experienced by 46.0% of the fruquintinib group in FRESCO as compared to 8.3% of the equivalent group in FRESCO-2.

An overview of treatment-emergent AESIs in FRESCO and FRESCO-2 is presented in Table 25, Document B of the CS. Higher proportions of participants experienced treatment-emergent AESIs in FRESCO (92.4% and 54.0%, respectively) than in FRESCO-2 (80.7% and 53.0%, respectively). Grade ≥3 AESIs were experienced by 43.9% and 12.4% of participants, respectively, in FRESCO and 37.1% and 19.1%, respectively, in FRESCO-2.

The most frequently reported TEAEs in FRESCO and FRESCO-2 are presented in Table 24, Document B of the CS. In FRESCO, the most frequently reported TEAEs in the fruquintinib arm were hypertension (57.2%), hand-foot syndrome (49.3%) and

proteinuria (43.2%); in the placebo arm, proteinuria (24.8%), elevated aspartate aminotransferase (17.5%) and hypertension (15.3%). In the fruquintinib group of FRESCO-2, the most frequently reported TEAEs were hypertension (36.8%), asthenia (34.0%) and decreased appetite (27.2%). In the placebo group, asthenia (22.6%), nausea (18.3%) and decreased appetite (17.4%) were most commonly reported.

Overall, the EAG's clinical expert is satisfied that the range and grade of adverse events reported in the CS are as expected from clinical use of fruquintinib in these patients and has no concerns.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

A summary of the eight RCTs included in the NMA is presented in Table 11 below. Detailed baseline characteristics for all studies are summarised in Appendix 1.

Table 11 Summary of RCTs included in the NMA [adapted from Table 16, Document B and Table 68, Appendix D of the CS]

Study ID	Intervention, N	Comparator, N	Lines of prior treatment (study inclusion criteria)	OS outcome definition	PFS outcome definition
FRESCO	Fruquintinib + BSC (n=278)	Placebo + BSC (n=138)	Failure of ≥2 lines of standard chemotherapies for advanced disease	Time from randomisation until death	Time from randomisation to disease progression or death
FRESCO-2	Fruquintinib + BSC (n=461)	Placebo + BSC (n=230)	Number of lines of prior treatment not specified, inclusion based on receiving all required treatments[†]	Time (months) from date of randomisation to death from any cause	Time (months) from randomisation until the first progressive disease or death from any cause
Xu 2017	Fruquintinib + BSC (n=47)	Placebo + BSC (n=24)	Failure of ≥2 lines of standard therapy (not specific to metastatic disease)	NR	PFS until the date of first documented progression or date of death from any cause, whichever came first
CONCUR	Regorafenib + BSC (n=136)	Placebo + BSC (n=-68)	Failure of ≥2 lines of previous treatment (not specific to metastatic disease)	Time from randomisation to death from any cause	Time from randomisation to first radiological or clinical finding of disease progression or death from any cause
CORRECT	Regorafenib + BSC (n=505)	Placebo + BSC (n=255)	Number of lines of prior treatment not specified; inclusion based on receiving all required treatments	Time from randomisation to death from any cause	Time from randomisation to first radiological or clinical observation of disease progression or any-cause death
Yoshino 2012	Trifluridine-tipiracil + BSC (n=114)	Placebo + BSC (n=58)	History of ≥2 lines of standard chemotherapy (not specific to metastatic disease)	Time between randomisation and death from any cause or the date of last follow-up	Time between randomisation and disease progression or death from any cause

Study ID	Intervention, N	Comparator, N	Lines of prior treatment (study inclusion criteria)	OS outcome definition	PFS outcome definition
RECOURSE	Trifluridine-tipiracil + BSC (n=534)	Placebo + BSC (n=266)	Failure of ≥2 lines of standard chemotherapies for metastatic disease	Time from randomisation to death from any cause	Time from randomisation to the first radiologic confirmation of disease progression or death from any cause
TERRA	Trifluridine-tipiracil +BSC (n=271)	Placebo + BSC (n=135)	Failure of ≥2 lines of standard chemotherapies for metastatic disease	NR	Calculated from the beginning of treatment to the time of disease progression or death from any cause.

Key: BSC, best supportive care; NR, not reported; OS, overall survival; PFS, progression free survival

In the NMA, the two FRESCO trials are entered separately but at other points in the company submission the FRESCO trials have been pooled. The EAG are happy with both approaches used by the company. The evidence presented in section B.2.8 supports pooling the FRESCO trials.

It is also the opinion of the EAG clinical expert that the two trials can be combined as the FRESCO trial would be similar to UK practice and the FRESCO2 trial is conducted in a population similar to the UK. The EAG agrees with the company's advisors to include all available randomised evidence in the NMA. The EAG have reviewed the information on the trials provided in Appendix D Table 68 and are happy that the definitions of OS and PFS are consistent between the different studies used in the NMA. The EAG are also satisfied that the information presented in Appendix D Table 70 indicates that the fruquintinib, regorafenib, and trifluridine-tipiracil trials used the same dose of the respective treatment.

The EAG considers the information presented in Tables 71 and 72 of Appendix D and highlights the company's acknowledgement of differences in participant characteristics between the studies, such as prior bevacizumab, Asian population, number of prior regimens, metastatic sites, liver metastases and ECOG status. The EAG considers the investigation of treatment effect modification through subgroup analyses outlined in sections B.2.9.3 and B.2.9.6 of the CS to be thorough sensitivity analyses of the treatment effect estimates. These procedures are also consistent with those used in earlier technology appraisals. The EAG reviewed Figures 22 to 27, which show the different subgroup analyses exploring differences between participants' characteristics in the studies included in the NMA. The treatment effects for fruquintinib vs. BSC in all subgroup analyses are consistent with those obtained from the NMA. Apart from the situation where no prior anti-VEGF treatment was used, the treatment effects for fruquintinib vs. regorafenib and trifluridine-tipiracil are consistent with those obtained from the NMA; however, these data should be interpreted with caution due to the small patient numbers informing these analyses.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The EAG is happy with the NMA methods used by the company and agrees that these are consistent with the recommendations of the NICE decision support unit. The EAG were able to reproduce the results of both fixed effects NMA presented by the

company. The EAG were pleased with the level of detail provided by the company in Appendix D section D.5 and reviewed the information in Tables 80 and 81 of Appendix D, which showed that similar results would have been obtained had random-effects been used rather than a fixed effects NMA.

3.5 Additional work on clinical effectiveness undertaken by the EAG

The EAG were able to replicate the results of the NMA of overall survival reported in Table 19, section B.2.9.5.1 and progression free survival shown in Table 21, section B.2.9.5.2.

3.6 Conclusions of the clinical effectiveness section

The EAG does not have any concerns regarding the clinical effectiveness section of the company submission. The information on adverse events was reviewed and there are no concerns regarding the safety profile of fruquintinib. It is the opinion of the EAG that the clinical effectiveness presented on the pooled FRESCO and FRESCO-2 studies was appropriate and demonstrates superiority of fruquintinib over best supportive care in terms of both overall and progression-free survival. The EAG also consider the comprehensive NMA shows fruquintinib to have a similar overall survival effect to both trifluridine-tipiracil and regorafenib and to be superior to both in terms of the effect on progression-free survival.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The details of the methods, results and quality assessment of the systematic review that the company conducted to identify economic evaluations mCRC are reported in section B.3.1 and appendix G of the company submission. Searches were conducted on the 23rd of October 2023 and there were no restrictions by geographical region. The review included economic evaluations of treatments specified in the NICE final scope for the population of interest and the review focussed in particular on analyses conducted from a UK perspective as these studies were the most relevant for informing the decision problem. Of the 41 identified publications, four economic evaluations were conducted from a UK healthcare perspective.[43-46] These included one peer-reviewed publication[45] and three health technology assessment (HTA) submissions (two for NICE, TA405and TA866, and one for SMC).[43, 44, 46] A summary of the economic evaluations is presented in Table 28 of the company submission document B. Three studies compare regorafenib with trifluridine-tipiracil[43-45] and one compared regorafenib with BSC.[46]

The EAG notes that the company undertook a thorough review of the published economic evidence relevant to this appraisal. The EAG sought clarification for the date when the systematic review was conducted as two different dates were reported in the company submission. The company clarified that the electronic database searches for the economic SLR were conducted on 4th October 2023, and grey literature searches were conducted on 26th October 2023. The EAG was satisfied with the clarification provided.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The EAG's assessment of the company submission against the NICE reference case is summarised in Table 12 below.

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Aligns with the reference case. Health effects were measured using life years and QALYs derived from OS and PFS survival curves.
Perspective on costs	NHS and PSS	Aligns with the reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligns with the reference case. A fully incremental analysis was conducted as per the reference case but based on feedback from clinical experts in the UK the company assumed that regorafenib would be the most relevant comparison. Pairwise analyses were also conducted.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with the reference case. A 10-year time horizon was applied. This took into account that fewer than 0.5% of patients remained alive in the company's base case model at 10 years.
Synthesis of evidence on health effects	Based on systematic review	Aligns with the reference case. Fruquintinib and BSC OS and PFS evidence is based on joint survival models from pooled FRESCO[29] and FRESCO-2 data.[34] Regorafenib and trifluridine-tipiracil OS and PFS are obtained from an NMA.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Aligns with reference case. QALYs calculated using EQ-5D-5L data mapped to 3L from the FRESCO-2 study[34]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligns with the reference case. HSUVs based on patient reported responses to the EQ-5D-5L from the FRESCO-2 study
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligns with the reference case

Element of health technology assessment	Reference case	EAG comment on company's submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligns with the reference case. Severity weightings, based on QALY shortfall analysis were applied.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Partially aligns with the reference case. Drug tariff prices, obtained from BNF are used in the model for concomitant medications, but the EAG considers eMIT prices to be more appropriate as most prescribing will take place in secondary care.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with the reference case

Key: BSC, best supportive care; EQ-5D, standardised instrument for use as a measure of health outcome; OS, overall survival; PFS, progression free survival; PSS, personal social services; QALYs, quality-adjusted life years

4.2.2 Model structure

A *de novo* cost-effectiveness model, developed in Microsoft Excel using an area-under-the-curve, partitioned survival analysis (PartSA) structure was submitted by the company (Figure 28 in company submission document B). The model has three mutually exclusive health states: progression free, progressed disease and death. Health state occupancy over time is informed directly by the area under the OS (proportion of patients who are alive) and PFS (proportion of 'progression-free' patients) curves for each comparator. The proportion of patients who are alive with progressed disease, and hence reside in the 'post-progression' health state, is calculated as the area between the OS curve and the PFS curve. Costs and QALYs were accrued according to the proportion of patients in the 'progression-free' and 'post-progression' health states over time. For fruquintinib, regorafenib and trifluridine-tipiracil, the proportion of the cohort progression free at any one time was split into the proportion on and off treatment. The proportions on and off treatment were based on TTD curves for fruquintinib and based on PFS HRs from the NMA for regorafenib and trifluridine-tipiracil. As PFS and OS were modelled independently (i.e. using independent parametric functions) the extrapolated PFS curve was capped by the OS curve to retain face validity and prevent the PFS curve from being able to

lie above the OS curve. PFS and OS were further capped by general population mortality informed by life tables for England and Wales[47] to ensure that modelled patients did not have a lower risk of death compared with the general population.

The EAG is satisfied that the use of a PartSA model structure is appropriate to model late-stage mCRC, particularly given that there is likely to be only one further line of treatment in the post-progression state. Specific description and critique of the data and assumptions used to derive OS, PFS and TTD extrapolation curves are discussed in section 4.2.6.

4.2.3 Population

The patient population is defined as [redacted] The base case modelled population (mean age 59 proportion male 58%) reflects the population of the pooled FRESCO and FRESCO-2 studies.

The EAG's full assessment of the study populations is provided in Section 3.2.1. Whilst the EAG note that the FRESCO study, conducted solely in China, may not be generalisable to the UK setting in terms of participant ethnicity, it was more generalisable than FRESCO-2 in terms of low rate of exposure to anti VEGF treatments (e.g. prior bevacizumab) and their fitness was likely more aligned with UK clinical practice in terms of clinical severity (i.e. 25% of patients with PS0 at baseline compared to 45% in FRESCO-2). On the other hand, the population characteristics of FRESCO-2 were more similar to the UK population with regard to age, race and geographical area and importantly, the FRESCO-2 study provides the data for EQ-5D utilities used in the model. FRESCO-2 patients were more heavily pretreated than those in FRESCO which might lead to worse prognosis than for those who have had fewer treatments.

The EAG notes that there are several model parameters that are impacted on by the decision to use FRESCO or FRESCO-2 data, namely (body surface area for calculation of trifluridine-tipiracil treatment acquisition costs; overall and

progression free survival, adverse events and subsequent treatment costs). The EAG notes that the company has provided a range of scenario analyses and functionality within their model to explore these uncertainties in detail. Given that neither study perfectly matches the UK population, the EAG considers it appropriate to pool the data sources for the base case analysis and to explore the impact of each individual study on cost-effectiveness results in scenario analyses.

4.2.4 Interventions and comparators

Section B.3.2.8.1 describes the intervention considered in this analysis as fruquintinib, which is administered orally at a recommended dose of 5 mg QD following a dosing schedule of three weeks on and one week off as per the dosing regimen received in FRESCO[29] and FRESCO-2,[34] and the anticipated marketing authorisation for fruquintinib, combined with BSC.

The EAG is satisfied that the intervention dosing costed in the company's economic model is aligned with the dosage used in the FRESCO[29] and FRESCO-2[34] studies. The EAG notes that fruquintinib does not currently have a marketing authorisation in the United Kingdom (UK). The process of seeking regulatory approval by the Medicines and Healthcare products Regulatory Agency (MHRA) is ongoing and a decision is expected [redacted]

The first comparator is regorafenib, administered orally at the SmPC recommended dose of 160 mg (4 x 40 mg tablets) QD for 3 weeks followed by 1 week off therapy until there is no observed benefit or until unacceptable toxicity occurs. This dose is also aligned with dosing schedules in the CORRECT[48] and CONCUR[49] clinical trials. The second comparator is trifluridine-tipiracil 35 mg/m^2 of body surface area, administered orally twice daily, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period. This treatment cycle is repeated every 4 weeks until disease progression or unacceptable toxicity. This dose is also aligned with the dosing schedule in the TERRA and RECOURSE clinical trials and the SmPC for trifluridine-tipiracil.[50] The third comparator, BSC was modelled as per the definition in the FRESCO[29] and FRESCO-2[34] trial protocol as any treatment necessary for health and not anticipated to interfere with study drug and was determined locally by the investigator.

The EAG is satisfied that the company has included the relevant comparators specified in the scope. The EAG is generally satisfied that the treatment dosages in the model are aligned with SmPC recommendations for the intervention and comparators and are broadly similar to how treatment would be delivered in UK clinical practice. The costing approach is also aligned with previous NICE technology appraisals for trifluridine-tipiracil (TA405)[44] and regorafenib (TA866).[43]

4.2.5 Perspective, time horizon and discounting

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS). The cost-effectiveness analysis adopts a 10-year time horizon, which was considered long enough to adequately capture the lifetime of patients that are modelled, in the company base case analysis to have a less than 0.5% chance of being alive at 10 years. The model uses a 1-week cycle length, which is assumed to be short enough to adequately capture meaningful changes in health status for patients with mCRC, who have been previously treated with or no considered candidates for the specified therapies in section B.3.2.1. A half-cycle correction is applied. Health effects were measured in quality-adjusted life years (QALYs) with a 3.5% discount applied to costs and QALYs.

The EAG is satisfied with the modelling perspective adopted by the company and that the 10-year time horizon is sufficient to capture all the benefits and costs of this population as the EAG's clinical expert agrees that it unlikely that any patients in this population will be alive at 10 years. A 5-year time horizon is explored in scenario analyses but only has a minimal impact on the ICER because 0% of the cohort are modelled to remain alive after 10 years. Discounting has been appropriately applied in line with the NICE reference case.[52]

4.2.6 Treatment effectiveness and extrapolation

Overall and progression free survival – fruquintinib and BSC

For the trial comparators, fruquintinib and BSC, data for long-term extrapolation were pooled across the FRESCO[29] and FRESCO-2[34] studies. The company base case analysis assumes that the proportional hazards assumption holds true, that there is no violation of the accelerated failure time assumption. Given the assumed constant treatment effect over time, the company used joint parametric survival models fitted

to pooled KM data from the trials, applying a modelled HR for fruquintinib versus BSC to extrapolate OS and PFS curves and derive expected long-term life years gained, QALYs and costs over the model time horizon. Scenario analyses explored the impact on cost-effectiveness of fitting independent survival curves to each arm.

For the joint parametric models, the company compared a full range of parametric survival curves fitted to the pooled data. The company sought clinical expert opinion, KM data, AIC and BIC for each survival curve and modelled outputs at 1,2, and 5 years for fruquintinib and BSC are provided for OS and PFS in Tables 13 and 14, respectively. The company selected a generalised gamma and log normal model for OS and PFS respectively.

Table 13 Comparison of statistical goodness of fit, company clinical expert opinion and modelled outcomes for different joint overall survival extrapolations for fruquintinib and BSC

Model	Statistical fit		OS landmarks			Median (months)
	AIC	BIC	1 year	2 years	5 years	
Fruquintinib (joint models) pooled data						
Company clinical expert opinion [A]	--	--	--	--	--	--
KM data	--	--	[redacted]	[redacted]	-	8.0
Exponential	7517.6	7527.6	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	7384.6	7399.6	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	7459.1	7474.1	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	7339.6	7354.6	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	7335.4	7350.4	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	7358.8	7373.9	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	7335.5	7355.5	[redacted]	[redacted]	[redacted]	[redacted]
BSC (joint models), pooled data						
Company clinical expert opinion [A]	--	--	--	4%	0%	--
KM data	--	--	[redacted]	--	--	5.5
Exponential	7517.6	7527.6	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	7384.6	7399.6	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	7459.1	7474.1	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	7339.6	7354.6	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	7335.4	7350.4	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	7358.8	7373.9	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	7335.5	7355.5	[redacted]	[redacted]	[redacted]	[redacted]
TA405 model result*	--	--	--	4.1%	0.6%	5.3
TA866 model result‡	--	--	18.0%	--	0.1%	5.5

†10.4% at 23 months, *Using a stratified log logistic joint model. ‡Using a generalised gamma joint model. [A] Detailed advisory board minutes have not been provided to the EAG. Where possible, company expert opinion has been obtained from the text of the company submission for information.
Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; KM, Kaplan-Meier; OS, overall survival.

Table 14 Comparison of statistical goodness of fit, company clinical expert opinion and modelled outcomes for different joint progression free survival (PFS) extrapolations for fruquintinib and BSC

Model	Statistical fit		PFS landmarks				
	AIC	BIC	6 months	1 year	2 years	5 years	Median (months)
Fruquintinib (joint models) pooled data							
Company clinical expert opinion [A]	--	--	--	--	0%	--	--
Observed KM data	--	--	[redacted]	[redacted]	–	–	3.7
Exponential	7296.2	7306.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	7040.6	7055.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	7249.0	7264.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	6864.9	6879.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	6866.7	6881.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	6949.1	6964.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	6867.4	6887.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (joint models), pooled data							
Company clinical expert opinion [A]	--	--	--		0%		--
KM data	--	--	[redacted]	[redacted]	–	--	1.6
Exponential	7296.2	7306.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	7040.6	7055.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	7249.0	7264.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	6864.9	6879.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	6866.7	6881.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	6949.1	6964.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	6867.4	6887.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA405†	--	--	--	--	--		1.7
TA866‡	--	--	--	0.2%			

Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; KM, Kaplan-Meier.
†Using a generalised gamma joint model. ‡Using a generalised gamma joint model. [A] Detailed advisory board minutes have not been provided to the EAG. Where possible, company expert opinion has been obtained from the text of the company submission for information.

The EAG raise three points of critique with regards to the modelling of fruquintinib and BSC OS and PFS.

<u>EAG view on pooling FRESCO and FRESCO-2 data to model OS and PFS</u>
As described in Section 4.2.3, the EAG agrees that the company's decision to pool FRESCO[29] and FRESCO 2[34] data for the base case cost-effectiveness analysis is appropriate but notes some important differences with FRESCO more generalisable in terms of disease severity and FRESCO-2 more generalisable in terms of participant characteristics. Given these potential concerns, the company provided a detailed set of analyses, including a full range of parametric survival curves, fitted independently to each data source to allow a full exploration of uncertainty. Modelled parameters are provided in response to clarification queries B4.

The EAG agrees with the decision to pool data for the base case, but also considers it appropriate to consider the variation in the ICER reported in the company's scenario analyses conducted at clarification stage (see response B4) using each study individually to give a more comprehensive assessment of the uncertainty surrounding the ICER. The EAG is satisfied that the decision to use either FRESCO or FRESCO-2 individually, compared to the pooled data for OS and PFS does not have a major impact on the ICER, with FRESCO slightly favouring BSC and FRESCO-2 slightly favouring fruquintinib.

<u>EAG view on selection of parametric survival curves for the joint models:</u>
The EAG is satisfied that the company's selection of parametric survival curves for OS and PFS is based on sound, rigorous methods, validated where possible with clinical expert opinion. The EAG's clinical expert is also of the view that the selected curves are reasonable. However, it is noted that, for BSC, all OS curves with a good statistical fit to the data (based on AIC and BIC) generate a slight under-estimation of OS at 1 year when compared to the KM data, which may generate a bias in favour of fruquintinib. It may therefore be reasonable to also consider independently fitted OS curves for fruquintinib and BSC separately.

EAG view on the appropriateness of joint versus independently fitted OS and PFS survival curves:

The EAG is satisfied that the company's process for deciding on whether the proportional hazards assumptions hold for OS and PFS follows best practice recommendations. However, there is some uncertainty surrounding the conclusion drawn by the company. Specifically for OS, for the pooled data across the FRESCO and FRESCO 2 studies, the company inspected log-cumulative hazard, Schoenfeld residual, quantile-quantile, and smoothed hazard plots (see Figures 30-33 of the company submission). The EAG is satisfied that the log-cumulative hazards plots do not cross, suggesting that the PH assumption may be reasonable. The quantile-quantile plot is a reasonably straight line, indicating no violation of the accelerated failure time assumption. The company note that the smoothed hazard plots take similar shapes with hazards increasing initially, and then decreasing over time. The EAG accepts that this is the case for OS, but further notes that the global PH test produced a p-value <0.05, suggesting a violation of the PH assumption. Whilst the EAG accepts that, on balance, the PH assumption seems reasonable for OS, that conclusion is not without uncertainty.

For PFS, a similar approach to deciding on whether the PH assumption is appropriate was followed by the company. For PFS, log-cumulative hazard plots cross at the start of the plot, quantile-quantile plots are non-linear, smoothed hazard plots cross, and the PH test was significant. Therefore, on balance, the EAG is of the view that the PH assumption is not supported for PFS.

The company provided a scenario analysis applying the best fitting independent survival curves to each arm of the pooled FRESCO and FRESCO 2 data in a scenario analysis. For fruquintinib, a log-normal was used for both OS and PFS, whereas for BSC a log-normal was used for OS and A log-logistic for PFS. At clarification, the EAG requested further details from the company, including exploration of a full range of parametric survival curves fitted independently to each arm of the pooled FRESCO and FRESCO 2 data. This information was provided in response to clarification queries B1 and fully integrated into the model by the company. Full details of the curve selection process are also provided in response to clarification queries B1. The EAG considers the company's process of selection and choosing of independently

fitted extrapolation curves for OS and PFS to be appropriate. The scenario analyses (clarification response B1) show that the decision to use joint versus independent models had the greatest impact on the OS curve for BSC, increasing the ICER for fruquintinib versus BSC by approximately £10,000. The impact on other OS pairwise comparisons or PFS was minimal. In summary, whilst the EAG accepts the company's assumption that the proportional hazards and accelerated failure time assumptions are likely to hold true for OS, this is less likely to be the case for PFS. Therefore, on balance, the EAG prefers the use of independently fitted curves, but there is uncertainty surrounding that conclusion. The EAG are of the view that both approaches should be considered for decision making.

Overall and Progression-free survival – regorafenib and trifluridine-tipiracil comparators

OS and PFS curves for regorafenib and trifluridine-tipiracil were obtained by applying HRs from a fixed effects NMA to the extrapolated fruquintinib OS and PFS curves. For OS, the fixed effect HRs used for the base case model were: regorafenib vs fruquintinib HR: 1.08 [95% CrI: 0.86, 1.33]; trifluridine-tipiracil vs fruquintinib HR: 1.05 [95% CrI: 0.87,1.28]). For PFS the HRs applied in the economic model were, regorafenib vs fruquintinib: 1.52 [95% CrI: 1.23, 1.85], trifluridine-tipiracil vs fruquintinib HR: 1.49 [95% CrI: 1.25, 1.82]).

The EAG is satisfied that the company has done a thorough assessment of heterogeneity and model fit. The EAG acknowledges that the company's decision to use of a fixed-effects NMA is based on the grounds that some comparators only have 2-3 studies and estimating between study heterogeneity for the RE model would be difficult. As the company use data from the FRESCO and FRESCO-2 trials for fruquintinib and BSC, the decision to use FE or RE does not impact the ICER versus BSC, but the EAG notes that the RE analysis leads to an increase of about £4,000 in the company's base case ICER versus trifluridine-tipiracil.

The company again assumed that the proportional hazards and accelerated failure time assumptions hold true across the different comparators included in the NMA, enabling the direct application of HRs. The company justified their preferred approach on the grounds that the use of the NMA aligns with the NICE methods guide, allows inclusion of the totality of the evidence, preserves randomisation from the trials and

aligns with the approach taken for TA886. Further details of curve selection including a discussion of why the company considers that the proportional hazards assumption is met, are provided in Section B.3.3.2 of the company submission.

The EAG notes that the approach taken for the company base case relies on applying a hazard ratio to an accelerated failure time survival curve for fruquintinib (i.e. generalised gamma in both the company and EAG preferred base cases for OS, and log normal for PFS). For this approach to be robust, an assumption of proportional hazards is required, and this assumption is not met for accelerated failure time survival curves. This would imply that selecting a curve that aligns with proportional hazards such as exponential would be more appropriate, but the EAG also agrees with the company that exponential and Gompertz curves are not a good fit to the underlying fruquintinib data.

As an alternative solution, at clarification queries, the EAG requested whether there were any Kaplan Meier curves available for regorafenib or trifluridine-tipiracil from the literature that could be digitised to allow an independent survival curve to be fitted to extrapolate OS and PFS for regorafenib and trifluridine-tipiracil. The company helpfully identified data from several studies for regorafenib (CORRECT and CONCUR data used for the assessment in TA866) and for trifluridine-tipiracil (pooled data from the RECOURSE and Yoshina trial used in TA405 and additional data from the TERRA trial). The company explained that regorafenib data couldn't be pooled for the CORRECT and CONCUR studies as this information was redacted from TA866. Available KM data from the published studies were digitised and a full range of survival curves were explored by the company in response to clarification queries B3. The most appropriate parametric survival curve was selected based on assessing visual fit to the KM data (see Figures 5 to 11of the company's response to clarification, statistical goodness of fit (See Tables 7, 13, 16 and 18) and the company's assessment of clinical plausibility. For the independently fitted curves, the company selected a generalised gamma for regorafenib OS a log normal for PFS. This decision was consistent with whether data from CORRECT or CONCUR were used to fit the curves. For trifluridine-tipiracil, again a generalised gamma was selected for OS and a log-normal for PFS.

The EAG is satisfied that the company's approach to selecting independently fitted curves is appropriate. Whilst one could argue for or against several different OS curves based on small differences in AIC, BIC and OS landmarks, the EAG is satisfied that the company's selections are reasonable. Similarly, for PFS, the EAG are satisfied that the curve selection process is appropriate. The EAG does however note that the modelled estimates of PFS for trifluridine-tipiracil are all substantially higher than the KM data would suggest (median PFS: 1.8 months versus company preferred curve 2.5 months and company base case from the pooled model 2.8 months). This may suggest an overestimate of progression free survival for trifluridine-tipiracil which would lead to a conservative assumption for the assessment of fruquintinib. The EAG notes that applying the digitised curves generally leads to a substantial reduction in the ICER for fruquintinib versus trifluridine-tipiracil with data from both the TERRA and pooled RECOURSE / Yoshino trials leading to increases in incremental QALY gains for fruquintinib. Similarly, whilst the conclusion of dominance remains for the independently fitted curves versus regorafenib, the magnitude of benefit is much higher when compared to the CORRECT study than when compared to the CONCUR study.

The EAG accepts that the company's preferred base case approach includes an assessment of the totality of the evidence, and this is a key strength of the approach taken. Additionally, the company's base case approach allows for the NMA model to control for variation in the characteristics of the underlying samples across trials, whereas the EAG suggested approach relies on a naïve comparison across studies. However, the EAG's approach has the advantage of not relying on a constant HR over time, which may not be a plausible assumption. Indeed, even though similar curves are fitted using the trial specific data, it is clear from the modelled outputs that a constant HR is not appropriate. It is also not appropriate to fit hazards ratios to extrapolation curves derived from non-proportional hazards models (i.e. log-normal). On balance, the EAG prefers the use of independently fitted survival curves, based on digitised KM data from the company's scenario analyses. For regorafenib, the EAG prefers the use of the CORRECT study data because it provides a larger sample size, the study characteristics are more aligned with those of the pooled FRESCO and FRESCO-2 studies and maintains consistency of source used for the EAG's preferred

approach to modelling time on treatment and RDI. For trifluridine-tipiracil, the EAG prefers to use the digitised data from the pooled RECOURSE and Yoshino studies.

The EAG accepts that our preferred approach also has limitations. It relies on a naïve comparison across the CORRECT, RECOURSE and FRESCO studies. However, on balance, the EAG considers it plausible to naively compare, based on similar justifications that the EAG supports the company's decision to pool the FRESCO and FRESCO-2 studies. To aid the committee in decision making, Appendix 1 provides a comparison of the baseline characteristics across all studies used in the network meta-analysis. The studies used in the EAG preferred economic model configuration, naïve comparison, are identified with an "", specifically pooled fresco study data (fruquintinib and BSC), CORRECT study data (regorafenib) and pooled Yoshino and RECOURSE study data (trifluridine-tipiracil). The company and EAG preferred assumptions for OS and PFS are compared in Table 15. The company and EAG preferred OS and PFS curves are compared in Figures 2 and 3, respectively.*

Table 15 Summary of modelled OS and PFS outputs for company and EAG preferred assumptions

	Proportion alive / progression free at 2 years				Mean modelled OS / PFS (undiscounted)			
	Fruquintinib	**Trifluridine-tipiracil**	**Regorafenib**	**BSC**	**Fruquintinib**	**Trifluridine-tipiracil**	**Regorafenib**	**BSC**
Overall survival								
Company base case [A]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pooled FRESCO and FRESCO-2 studies (ind. curves)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ind. Curves for comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case [B]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression free survival								
Company base case [C]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pooled FRESCO and FRESCO-2 studies (ind. curves)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ind. Curves for comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case [D]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[A] **Company preferred OS:** joint models (generalised gamma) from pooled FRESCO and FRESCO-2 data for fruquintinib and BSC; HRs from fixed-effects NMA for trifluridine-tipiracil and regorafenib.

[B] **EAG preferred OS:** independently fitted (generalised gamma) survival curves for fruquintinib and BSC; independently fitted (generalised gamma) survival curves from the CORRECT study (regorafenib) and the pooled RECOURSE and Yoshino studies (trifluridine-tipiracil).

[C] **Company preferred PFS:** joint models (log normal) from pooled FRESCO and FRESCO-2 data for fruquintinib and BSC; HRs from fixed-effects NMA for trifluridine-tipiracil and regorafenib.

[D] **EAG preferred PFS:** independently fitted (log-normal) survival curves for fruquintinib and BSC; independently fitted (log normal) survival curves from the CORRECT study (regorafenib) and the pooled RECOURSE and Yoshino studies (trifluridine-tipiracil).

Figure 2 Company versus EAG preferred overall survival curves

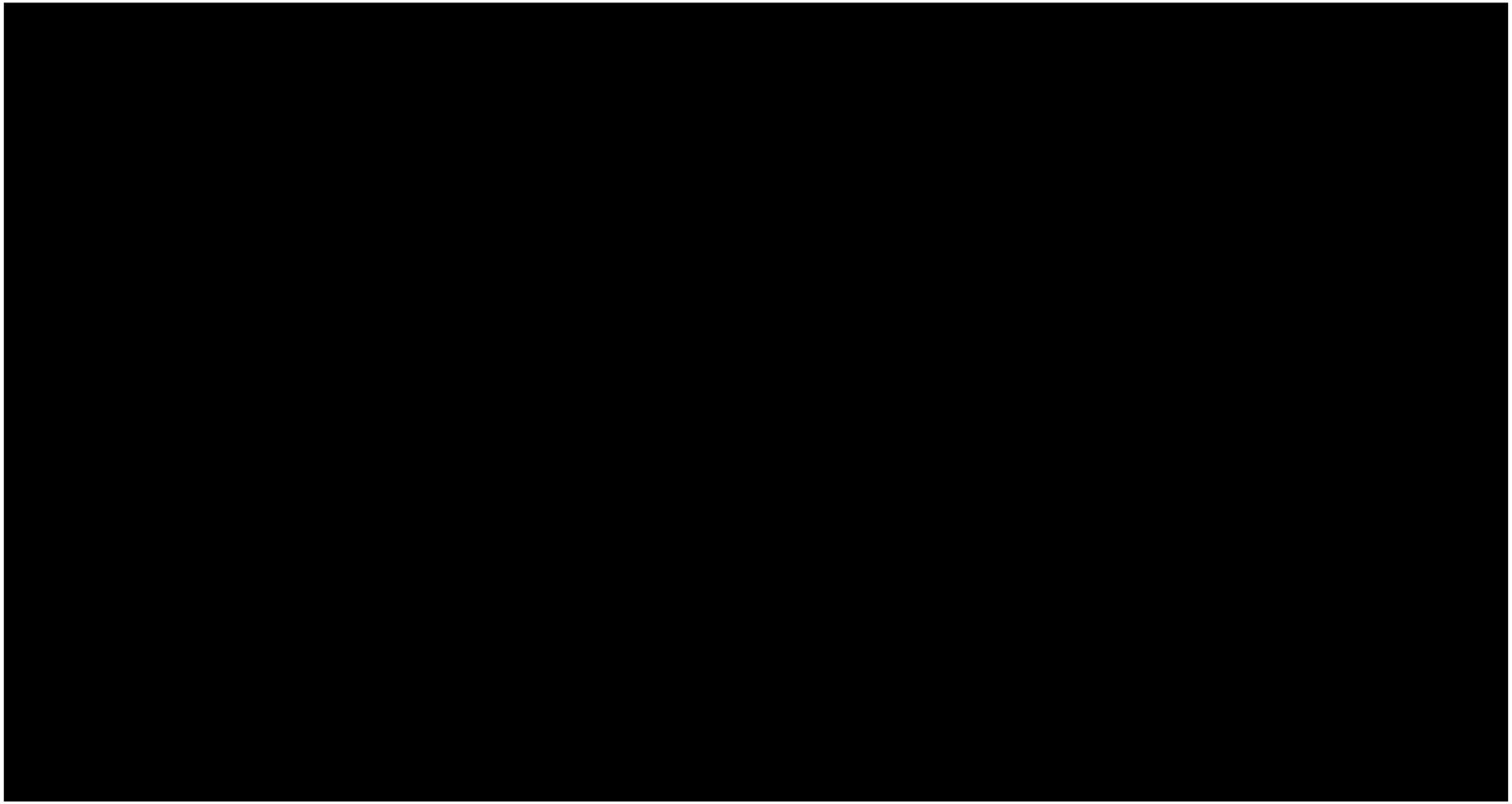


Figure 3 Company versus EAG preferred progression free survival curves

Time to treatment discontinuation

Based on clinical expert opinion elicited at the UK market access advisory board (1st December 2023) the company assumed that treatment beyond progression would not happen in UK clinical practice and, as a result, TTD curves were capped by PFS for fruquintinib and all comparators.[51] Given that TTD curves were not required for BSC, an independent model was fit to the fruquintinib TTD data only based on pooled data from the FRESCO and FRESCO-2 studies. Pooled TTD KM data were highly mature with 94% of patients having discontinued at the end of follow-up in the fruquintinib arm. The company reported that log-logistic, generalised gamma and log-normal curves provided the best statistical fit to the KM data based on AIC and BIC statistics and chose a log-normal curve for their base case analysis. A comparison of different TTD curves is provided in Table 16.

The EAG did not have access to the minutes of the advisory board meeting and therefore can only report what was included in the submission. The EAG notes that that the best fitting curve in terms of minimising AIC and BIC score, the log-logistic and generalised gamma curves are a better statistical fit for fruquintinib. The EAG observes that there is some overlap between the company preferred PFS and TTD curves, but that TTD has been capped at PFS in the company's economic model. All curves involve some overlap at 1 and 2 years of the estimated PFS curve. The EAG believes that this is likely to represent a conservative assumption for fruquintinib, particularly given that, in UK clinical practice, some patients, even if a small percentage will discontinue treatment prior to progression of their disease. Discontinuation may be for various reasons, including adverse events, patient preference etc. The EAG appreciates that the selection of different curves has minimal impact on the ICER and that the PFS and TTD curves converge at the tail where few patients remain progression free. Given that the generalised gamma curve provides a lower proportion on treatment at the tail of the curve, the EAG prefers this for decision making.

Table 16 Comparison of statistical goodness of fit, company clinical expert opinion and modelled outcomes for time to treatment discontinuation for different parametric survival curves

Model	AIC	BIC	6 months TTD	1 year TTD	2-year TTD	Median (months)
Company clinical expert opinion	--	--	--	--		--
Observed KM data	--	--	[redacted]	[redacted]	–	[redacted]
Exponential	5465.0	5469.6	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	5438.5	5447.7	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	5466.0	5475.2	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	5398.5	5407.7	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	5418.1	5427.3	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	5422.8	5432.0	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	5400.8	5414.6	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; KM, Kaplan-Meier; TTD, time to treatment discontinuation

Due to lack of publicly available data the company estimated TTD for regorafenib and trifluridine-tipiracil by applying the relevant PFS HRs from the fixed effects NMA for fruquintinib vs regorafenib: (HR: 1.52 [95% CrI: 1.23, 1.85]) and versus trifluridine-tipiracil: (HR: 1.49 [95% Crl: 1.25, 1.82]). In response to clarification queries, the company were able to identify digitised data for TTD from the pooled RECOURSE and Yoshino trials. In this scenario, the company apply a log-normal curve, aligned with the PFS curve, which was also be best fitting curve statistically.

The EAG does not consider the application of PFS HRs to TTD curves to represent a good approach to estimating treatment discontinuation. It assumes that the hazards of treatment discontinuation is proportional between treatments, and that the relationship is constant over time. This is unlikely to be the case because different treatments are likely to have different adverse event profiles, particularly regorafenib which may have higher initial treatment discontinuation rates than other comparators. The EAG prefers the company's scenario analysis which applies exponential treatment discontinuation curves based on median time to treatment discontinuation data from the trials for regorafenib (CORRECT study) and using the available digitised KM curves to fit survival models for trifluridine-tipiracil based on the pooled RECOURSE and Yoshino trials. Company and EAG preferred TTD curves are compared in Figure 4.

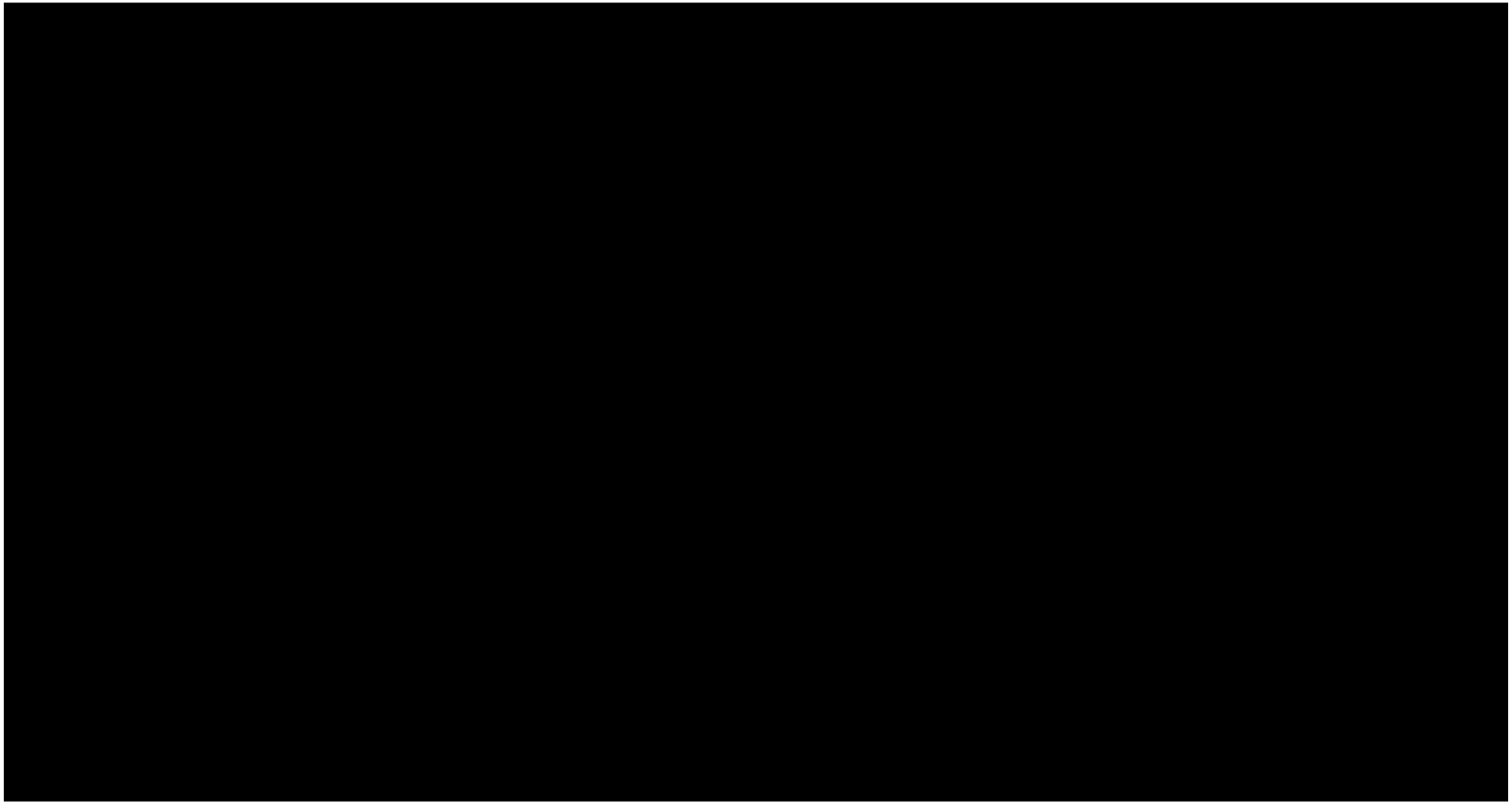


Figure 4 Company versus EAG preferred TTD curves

Adverse reactions

Grade 1 or 2 treatment-related TEAEs that occurred in at least 10% of patients, and Grade 3 or above treatment-related TEAEs that occurred in at least 2% of patients across any modelled treatment were considered. The company used the pooled data from FRESCO and FRESCO-2 to inform the proportion of patients experiencing AEs associated with fruquintinib and BSC. Treatment-related TEAEs for trifluridine-tipiracil and regorafenib were sourced from TA866;[43] proportions were based on pooled data from CONCUR[49] and CORRECT[48] for regorafenib, and RECOURSE,[53] TERRA[54] and Yoshino, 2012[40] for trifluridine-tipiracil. As Grade 1–2 adverse events were not reported in the trial publications for regorafenib and trifluridine-tipiracil, incidences were calculated using the difference between all treatment-related TEAEs and Grade 3 or above treatment-related TEAEs reported in the trial publications, as per the Committee's preferred approach in TA866.[43] The proportion of AEs in comparator trials were pooled and reweighted based on trial population size.

The EAG is satisfied that the company's approach to estimating adverse event rates is appropriate for decision making. Critique of AE disutilities and costs are described in Sections 4.27 and 4.2.8 respectively.

4.2.7 Health related quality of life

Utility values were included in the model for the progression-free and post-progression health states, with utility decrements applied separately to capture the impact of adverse events on quality of life.

HRQoL studies identified in literature review

A systematic literature review (SLR) identified 10 studies meeting the NICE reference case evidence requirements for health state utility values, with six studies identified as primary utility studies[55-60] and four were prior HTAs.[43, 44, 46, 61] The utility decrements associated with progressed disease from two of the prior HTAs[43, 44] were used in sensitivity analysis.

Health state utility values

Quality of life data were collected in FRESCO-2 using EQ-5D-3L and analysed using mixed-effects repeated-measures linear regression models for ITT patients with baseline and at least one post-baseline value (n=544). Progression status and baseline

utility were included as covariates in the multivariable analyses where the utility decrement for progressed disease ([redacted]) was statistically significant. No treatment-specific utility values were modelled, although it is unclear if this is due to there being no difference in utility values observed in the EQ-5D data collected. The health-state specific utility values were also appropriately adjusted for age and gender. Table 17 summarises the values included in the model alongside a comparison with values taken from other relevant HTAs, which were used to inform scenario analyses.

Table 17 FRESCO-2 EQ-5D-3L utility values (base case) compared with previous HTAs (scenario analysis) [adapted from Table 50, Document B of the CS]

Label	FRESCO-2	TA866	TA405
Progression-free	[redacted]	0.72	0.73
Post-progression	[redacted]	0.59	0.64
Progression decrement	[redacted]	-0.13	-0.09

Key: TA, technology appraisal.

Adverse event utility decrements

Adverse event disutilities were included in the model as one-off QALY decrements in the first model cycle (see Table 18 below). It was noted in the CS that the quality of life impact of adverse events may be captured to some extent through the EQ-5D-3L data collected in the FRESCO-2 trial, but equally patients may not have been experiencing adverse events at the time the EQ-5D data were collected. As such, utility decrements were included separately by combining the proportions of Grade 1 or 2 treatment-related TEAEs experience by ≥10% of patients and Grade 3 or above treatment-related TEAEs experienced by ≥2% of patients, with the disutilities derived from TA866. Most treatment-related TEAEs were assumed to have a 1-week duration in line with TA866 and TA405, except for diarrhoea (3 weeks) and reduced appetite (0.5 weeks).

Table 118 Total AE QALY decrement per treatment applied in the model

Treatment	Total AE QALY decrement
Fruquintinib	0.0009
Regorafenib	0.0015
Trifluridine-tipiracil	0.0030
BSC	0.0003

Key: AE, adverse event; BSC, best supportive care; QALY, quality-adjusted life year.

In general, the EAG was content with the company's approach to deriving utility values but would like to highlight the following points:

- *While the availability of trial-derived EQ-5D-3L data to estimate utility values is a strength of the analysis, the EAG notes that quality of life data were only collected in FRESCO-2, whereas efficacy data were derived from the pooled analysis of the FRESCO and FRESCO-2 studies. However, as the patient characteristics in FRESCO-2 were more representative of the UK population the quality-of-life data derived from this study for use in the model can be considered representative of the patient population likely to receive fruquintinib in UK clinical practice.*
- *The utility value used in the model for the post-progression health state appears high for the stage of disease and also when compared with the values used in previous TAs or relevant utility studies identified in the literature.[43, 44, 55, 60] This results in a relatively small quality of life decrement when patients experience progression ([redacted]) which may lack face validity. The impact of using alternative utility values from TA866 and TA405 where a larger utility decrement (0.13 and 0.09 respectively) was applied was explored in sensitivity analysis, showing any potential underestimation of the true quality of life impact of progression has a relatively minor impact on the results.*
- *The duration of adverse events was assumed to be 1 week on average for the majority of TEAEs included in the model to align with TA866 and T405, instead of using data from the FRESCO and FRESCO-2 studies. Upon request the company provided sensitivity analysis using the pooled FRESCO and FRESCO-2 clinical data for adverse event durations which had minimal impact on the results.*

4.2.8 Resources and costs

Costs in the model included treatment acquisition costs for fruquintinib, regorafenib and trifluridine-tipiracil, concomitant medication costs, subsequent treatment costs, health state costs, adverse event costs, and end-of-life care costs. Resource use unit costs were valued using NHS reference costs 2021/22,[62] Personal Social Services Research Unit (PSSRU) 2022[63] and preferred assumptions from relevant previous NICE technology appraisals (mainly TA866).[43] The medicine costs were sourced from the British National Formulary (BNF).[64]

Treatment acquisition costs

All primary treatments are given in 4-week treatment cycles. The model applied the full per-cycle costs of the medicines at the start of each 4-week treatment cycle regardless of whether patients stopped treatment at any point during the cycle, which reflects practice and is consistent with the approach taken in TA866.

Fruquinitib is given at a dose of 5mg once daily for 3 weeks followed by 1 week off. Regorafenib is given at a dose of 160mg per day (4x40mg tablets) for 3 weeks followed by 1 week off. For trifluridine-tipiracil the treatment cycle involves patients receiving 2 weeks of active treatment of 35mg/m^2 twice daily for 5 days followed by 2 days off per week, then 2 weeks off with dosage calculated based on body surface area (BSA). The methods of moments approach were used where a normal distribution was fitted to the mean BSA from the pooled FRESCO and FRESCO-2 trials to estimate patient weight distribution (CS Table 53).

The acquisition costs were adjusted to account for relative dose intensity (RDI) with an assumption made that RDI is likely to be similar between treatments in practice. In the CS the RDI calculated from the pooled FRESCO and FRESCO-2 trials (89.6%) was applied to all treatments to ensure consistency in RDI definition and to align with the assumptions in TA866. To further support this assumption the company cited RWE showing similar proportions of patients experience dose reductions with regorafenib and trifluridine-tipiracil (54% and 48% respectively).[65] The treatment costs for fruquintinib, regorafenib and trifluridine-tipiracil including the cost per treatment cycle are summarised in Table 19.

Table 19 Treatment costs (adapted from Table 52, Document B of the CS)

Drug	Dose	mg/tablet	Pack price	Pack size (number of tablets)	Cost per treatment cycle*
Fruquintinib (list price)	5 mg, once daily for 3 weeks, followed by 1 week off	5	£[redacted]†	21	£[redacted] (list price) [redacted] £[redacted] (PAS price)
Fruquintinib (PAS price)			£[redacted]‡		
Fruquintinib (list price)		1	£[redacted]†		
Fruquintinib (PAS price)			£[redacted]‡		
Regorafenib	160 mg, once daily for 3 weeks, followed by 1 week off	40	£3,744.00	84	£3,353.88
Trifluridine-tipiracil	35 mg/m^2 twice daily for 5 days, followed by 2 days off. Active treatment is given for 2 weeks, followed by 2 weeks off	15	£500.00	20	£1,815.04
		20	£666.67	20	

†Proposed list price of fruquintinib to be approved.
‡ Proposed PAS price of fruquintinib to be approved.
* Adjusted for relative dose intensity.
Abbreviations: PAS, patient access scheme.

Concomitant medication

Concomitant medication costs were assumed to represent the cost of BSC in the model with the same cost applied to each arm in line with clinical expert opinion that BSC cost is unlikely to vary by treatment. The costs were estimated based on medication received by ≥ 10% of patients in the pooled FRESCO and FRESCO-2 studies (CS Table 56) combined with the costs per week to give a weighted average cost of £9 per treatment cycle in the fruquintinib, regorafenib and trifluridine-tipiracil arms and £8 in the BSC arm.

Subsequent treatment costs

The company stated that the approach to modelling subsequent treatments was selected to align with the clinical pathway and the preferred assumptions in TA866 with a one-off cost applied at the point of progression. Due to the lack of data available on the proportion of patients receiving subsequent treatments in the trials for regorafenib and trifluridine-tipiracil, the proportions derived from the pooled FRESCO and FRESCO-2 trials for fruquintinib were applied to all active treatment arms (CS Table 59) with appropriate adjustments made to remove repeat use of initial treatment. The duration of subsequent treatment was set at 1 week to be consistent with the preferred assumptions in TA866 and TA405, increasing to 2 weeks in a scenario analysis. As some treatments received in FRESCO and FRESCO-2 are not recommended by NICE, a scenario analysis was also conducted using proportions estimated by clinical experts.

Health state unit costs and resource use

In line with the general approach taken by the company throughout the CS, the medical resource use estimates used in the model were consistent with those used in TA866. The CS noted that as no additional resource use data were identified in the SLR to those in NICE TA866, the resource use frequencies were sourced from TA866 and validated by UK clinicians at the company's market access advisory board (CS Table 63). A scenario was also presented using mean resource use estimates from UK clinicians. Disease management costs used in the company base case economic model are provided in Table 20.

Table 20: Disease management costs by health state (taken from the company model).

Health State	Disease Management Cost (per 1-Week Cycle)
Progression-free; active treatment	£139
Progression-free; BSC	£139
Post Progression	£61

Key: BSC, best supportive care

Adverse reaction unit costs and resource use

Adverse event costs were applied as a one-off cost in the first model cycle on the assumption that most adverse events are experienced at the start of treatment. The

one-off cost was estimated based on the Grade 1 or 2 TEAEs experience by ≥10% of patients and Grade 3 or above TEAEs experienced by ≥2% of patients combined with the unit cost of treating the adverse event. For fruquintinib and BSC treatment arms the proportions applied were taken from FRESCO and FRESCO-2 pooled data, whereas for regorafenib and trifluridine-tipiracil the proportions applied were taken from TA866. AE costs are summarised in Table 21.

Table 21: One-off cost of AEs, by treatment arm [reproduced from Table 65, Document B of the CS]

Primary treatment	Fruquintinib	Regorafenib	Trifluridine-tipiracil	BSC
Total cost of AEs	£180.10	£290.94	£630.60	£41.62

Key: AE, adverse events

End-of-life care costs

A one-off end-of-life care cost of £7,192 was included based on the health and social care costs for mCRC patients estimated by Round et al.[66] This is consistent with the cost applied in TA866.

The EAG notes that drug tariff prices obtained from the BNF was the source of medicine costs, but NICE have a preference for using eMIT costs where available. As some concomitant treatment medicine costs are available on eMIT, these costs are preferred for use in the model. A comparison of the BNF and eMIT costs is provided in Table 22 below.

Table 22: Comparison of BNF and eMIT costs for concomitant medicines

Medicine	Pack size	BNF price per pack	eMIT price per pack
Paracetamol 500mg	100	£2.34	£0.84
Ibuprofen 400mg	84	£2.87	£1.00
Lorazepam 1mg	28	£1.41	£3.36
Macrogol 3350 1mg	20	£3.29	£1.99
Dexamethasone 2mg	50	£3.13	£2.32
Metoclopramide 10mg	28	£0.35	£0.72
Furosemide 40mg	28	£0.57	£0.27

Medicine	Pack size	BNF price per pack	eMIT price per pack
Metoclopramide 10mg	28	£0.35	£0.36
Potassium chloride 20mg	30	£20.19	£3.42
Colecalciferol 400mg	60	£1.70	£0.63

Key: BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool

The EAG largely agrees with the company's approach to resource use whereby the committee preferred assumptions in TA866 were used in the model base case. While it is generally helpful to have this consistency across appraisals, it is also appropriate to consider whether those assumptions still apply once the medicine has been in use. On this basis, the EAG preferred some alternative assumptions as follows:

- *Clinical input to the EAG confirmed that an additional visit is required in cycle 1 for regorafenib treated patients, to check blood pressure and liver function. The CS included a scenario analysis where resource use estimates were based on clinical opinion; this scenario was considered more appropriate by the EAG as it included monthly tests for renal and liver function in the progression-free health state. Two additional outpatient visits in cycle 1 were added in the regorafenib arm in the EAG preferred base case to account for additional monitoring for toxicity and implementing required regorafenib dose-adjustments. The impact on the ICER was minimal.*
- *Subsequent treatments included in the base case were informed by the pooled FRESCO and FRESCO-2 studies to align with the efficacy data, but this resulted in some treatments being included that are not recommended by NICE (e.g. bevacizumab). An alternative scenario analysis based on proportions estimated by clinical experts was considered more reflective of practice. See table 23 for subsequent treatment assumptions applied in EAG preferred base case. Furthermore, the EAG questioned the validity of a one-week treatment duration, which was justified by the company at clarification on the basis of patients having poor prognosis and to align with the committee's preferred approach in TA405 and TA866. The EAG preferred*

approach increased treatment duration to two months informed by clinical expert input. These changes had a minor impact on the results.

Table 23 Subsequent therapies, EAG preferred base case assumptions [adapted from Table 60 of the CS]

Primary treatment	Proportion receiving subsequent anti-cancer treatment	Subsequent therapy: regorafenib (%)	Subsequent therapy: trifluridine-tipiracil (%)
Fruquintinib	10%	0%	100%
Regorafenib	5%	0%	100%
Trifluridine-tipiracil	10%	100%	0%
BSC	0%	0%	0%

Key: BSC, best supportive care.

- *Further clarification was requested from the company to support applying the RDI from the pooled FRESCO and FRESCO-2 trials to all treatment arms instead of modelling treatment-specific RDI separately from the respective trials for regorafenib and trifluridine-tipiracil (CORRECT and RECOURSE respectively). The company explained that definitions of RDI differed between the trials which would lead to inconsistent estimates. They also cited RWE for fruquintinib showing similar RDI in practice to the rate observed in FRESCO and FRESCO-2 (85.3%),[67] whereas the literature estimates for regorafenib and trifluridine-tipiracil suggested some variation in RDI in practice. Sensitivity analysis provided by the company using the available RDI rates from the respective trials for fruquintinib, regorafenib and trifluridine-tipiracil had a small impact on the results. The EAG agrees that while the different RDIs are likely largely driven by differing definitions of RDI across the trials, it is preferable to use the individual trial rates in the base case to ensure consistency with the efficacy estimates used in the model. A comparison of the different RDIs is provided in Table 24 below.*

Table 24 Comparison of RDIs used in base case and scenario analysis

	Fruquintinib	Regorafenib	Trifluridine/ tipiracil	Sources
Base case	89.6%	89.6%	89.6%	Pooled FRESCO[29] and FRESCO-2[34] trials applied to all treatments to ensure consistency in RDI definition and to align with the assumptions in TA866.
RDIs from individual trial data	89.6%	78.9%	89%	Treatment-specific RDIs applied from pooled FRESCO[29] and FRESCO-2,[34] CORRECT[58] and RECOURSE[53] trials
RDI from fruquintinib RWE data	85.3%	85.3%	85.3%	Li et al. RWE study of fruquintinib[67]

Key: RDI, relative dose intensity; RWE, real world evidence

The per-cycle cost of trifluridine/tipiracil applied in the model is lower than estimated in TA866 (£1,815 versus £2,071) due to different methods being used to estimate the cost in each appraisal. The methods of moments approach were used in this appraisal to estimate patient weight by fitting a normal distribution to the mean BSA from the pooled FRESCO and FRESCO-2 trial data. This compares to TA866 where a mean BSA estimate from a published study (Sacco) was used. It is likely the methods of moment approach produce a more accurate estimation of the cost of trifluridine/ tipiracil on the assumption that the patients in FRESCO and FRESCO-2 reflect those receiving treatment in practice.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company preferred base case results are presented in section B.3.11 of the company submission (document B). The presented results incorporate a proposed [redacted] PAS for fruquintinib and list prices for regorafenib and trifluridine-tipiracil. Results based on the list price for fruquintinib are presented in Appendix R of the company submission. Confidential discounted prices are available for regorafenib and trifluridine-tipiracil comparators. The impact of these prices on the ICER is considered by the EAG in a confidential appendix.

Over, the full model time horizon of 10 years, fruquintinib is more costly than trifluridine-tipiracil ([redacted]) and BSC [redacted] but less costly than regorafenib [redacted]. Modelled costs are most sensitive to the treatment acquisition, treatment related TEAE management, and disease management costs. The rest of the costs (concomitant medicines, subsequent treatment and end of life) were similar between all the interventions.

Fruquintinib was associated with improved mean OS (10.9 months) vs regorafenib, trifluridine-tipiracil and BSC (10.2,10.4 and 7.4 months, respectively), and improved mean PFS (4.6 months) vs regorafenib, trifluridine-tipiracil and BSC (3.4, 3.5 and 2.3 months, respectively). This translated into [redacted] total QALYs for fruquintinib, yielding an incremental QALY benefit vs regorafenib, trifluridine-tipiracil and BSC (total QALYs of [redacted], [redacted] and [redacted], respectively). The modelled incremental benefits for fruquintinib versus regorafenib and trifluridine-tipiracil were generated through a longer time spent in the pre-progression health state, with substantial gains over BSC in both pre and post progression states.

Given the severity of mCRC, QALY shortfalls apply to this assessment. QALY shortfall calculations are provided in Table 25 below for the company preferred base case analysis.

Table 25 Summary features of QALY shortfall analysis

Remaining QALYs	Regorafenib	Trifluridine/tipiracil	BSC
Without disease	12.89	12.89	12.89
With disease	0.57	0.58	0.42
Absolute QALY shortfall	12.32	12.31	12.48
Proportional QALY shortfall	95.57%	95.50%	96.78%
QALY weight	x1.7	x1.7	x1.7

Results of the company's preferred base case deterministic and probabilistic analyses are provided in Table 26 (fully incremental) and Table 27 (pairwise of fruquintinib versus comparators). Based on the QALY shortfall analysis, the most appropriate severity weighting is x1.7 for all comparisons, based on a proportional QALY shortfall of > 95%. This finding is consistent whether the company or EAG scenarios are preferred. The EAG considers that the results from the cost-effectiveness modelling should be interpreted with a weighting of 1.7 applied to all incremental QALYs. Weightings of 1.0 and 1.2 are also provided for the committee's information. The CEACs and cost-effectiveness plane for fruquintinib vs the comparators are presented in Figures 5 and 6, respectively. The probabilistic analyses show that fruquintinib was associated with a probability of cost-effectiveness of [redacted] at a threshold value of £51,000 per QALY, with the £51k threshold implying a severity weighting of 1.7 applied to a £30K threshold. The company explain that uncertainty in the probabilistic results for fruquintinib vs regorafenib and trifluridine-tipiracil may be overestimated because HRs were sampled independently for OS and PFS curves.

The EAG accepts the point that sampling from joint distributions for PFS and OS would be ideal, but difficult to achieve in the partitioned survival structure. However, even with this uncertainty, the probability of cost-effectiveness at the upper range of the typical threshold remains low for the company's base case and majority of scenario analyses.

Table 26 Base case analyses (fully incremental) conducted by the company [reproduced from Tables 72 and74 of Document B of the CS and Table 41 of the company's clarification response]

Intervention	Total Costs £	Total Lys	Total QALYs	Incremental Cost	Incremental QALY 1.0	Incremental QALY 1.2	Incremental QALY 1.7	ICER 1.0	ICER 1.2	ICER 1.7
Base case results (fully incremental analysis) – PAS price										
BSC	[redacted]	[redacted]	[redacted]							
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine/tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case results, probabilistic sensitivity analysis (fully incremental)										
BSC	[redacted]	-	[redacted]							
Regorafenib	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine/tipiracil	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 27 Company preferred deterministic and probabilistic base case assumptions (pairwise comparisons) [reproduced from Tables 72 and 74, Document B of the CS and Table 42 of the company's clarification response]

Technologies	Total costs (£)	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs x1 weighting	Incremental QALYs x1.7 weighting	Pairwise ICER x1 weighting	Pairwise ICER x1.7 weighting
Deterministic analysis								
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	–	–		–		–
Probabilistic analysis								
BSC	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	–	-	-	–	-	–

Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs quality adjusted life years.

Figure 5 Company's preferred base case analysis, cost effectiveness acceptability curve

Figure 6 Company's preferred base case analysis, cost effectiveness plane

5.2 Company's sensitivity analyses

The company also undertook several univariate sensitivity analyses to address parameter uncertainty in the model. Due to the similarity in outcomes between treatments NHB was recorded at the upper and lower levels to produce a tornado diagram. Results of the 10 most influential parameters are presented in tables 75-77 of the company submission. The company also conducted a range of scenario analyses and the summary of scenario analysis performed with justification is presented in

section B.3.12.3 in the company submission document B. The results of a full range of scenario analyses conducted by the company for their original submission and in response to clarification queries are reproduced in Table 28 (unweighted QALYs) and Table 29 (QALY severity weighting of 1.7 applied) below.

Table 28 Deterministic pairwise scenario analysis results (QALYs unweighted)

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)
Base-case	[redacted]								
Discount rate 0% for Costs and outcomes	[redacted]								
Discount rate 1.5% for Costs and outcomes	[redacted]								
Time Horizon 5 years	[redacted]								
OS (Joint curves) - log-logistic	[redacted]								
OS (Joint curves) - log-normal	[redacted]								
OS (Joint curves) - Weibull	[redacted]								
OS (Joint curves) - Exponential	[redacted]								
OS (Joint curves) - Gompertz	[redacted]								
OS (Joint curves) - Gamma	[redacted]								
PFS (Joint curves) - log-logistic	[redacted]								
PFS (Joint curves) - generalised gamma	[redacted]								
PFS (Joint curves) - Weibull	[redacted]								
PFS (Joint curves) - Exponential	[redacted]								
PFS (Joint curves) - Gompertz	[redacted]								
PFS (Joint curves) - Gamma	[redacted]								
OS (individual fits: fruquintinib and BSC) - Best fitting	[redacted]								
PFS (individual fits: fruquintinib and BSC) - best fitting	[redacted]								
Treat to progression	[redacted]								
Grade 1-2 AEs excluded	[redacted]								
Subsequent treatments from clinical opinion	[redacted]								

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)
Subsequent treatments: 2-week duration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from Pooled FRESCO and FRESCO-2 for BSC arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use: based on clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 disutility as per Grade 3 for clinically identified AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA866	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA405	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post EAG clarification queries analyses									
EAG QB1. Independent curves OS - gen gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB1. Independent curves OS - log normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB1. Independent curves PFS - log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB1. Independent curves OS - log normal; PFS - log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB1. Independent curves OS - gen gamma; PFS - log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB2. Random effects NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB3. Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and regorafenib (CORRECT) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)
EAG QB3. Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and regorafenib (CONCUR) data	[redacted]								
EAG QB3. Digitised trifluridine-tipiracil (TERRA) and regorafenib (CORRECT) data	[redacted]								
EAG QB3. Digitised trifluridine-tipiracil (TERRA) and regorafenib (CONCUR) data	[redacted]								
EAG QB4. Use FRESCO data only	[redacted]								
EAG QB4. Use FRESCO-2 data only	[redacted]								
EAG QB7. Use mean AE duration data from Pooled FRESCO and FRESCO-2 trials	[redacted]								
EAG QB9. Use RDI from respective trials	[redacted]								
EAG QB10. Apply alternative RDI for all treatments	[redacted]								
EAG QB11. Subsequent therapy proportions from clinical opinion + 10% of patients receiving subsequent therapy	[redacted]								
EAG QB12. Subsequent therapy duration: 8 weeks	[redacted]								
EAG QB12. Subsequent therapy duration: 4 weeks	[redacted]								

Key: Dominant means costs less and is more effective. AE, adverse event; BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal.

Table 29 Deterministic pairwise scenario analysis results (QALY severity weighting of 1.7 applied).

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)
Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 0% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 1.5% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time Horizon 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS (Joint curves) - Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (Joint curves) - Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS (individual fits: fruquintinib and BSC) - Best fitting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS (individual fits: fruquintinib and BSC) - best fitting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treat to progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 AEs excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)
Subsequent treatments: 2 week duration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from Pooled FRESCO and FRESCO-2 for BSC arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use: based on clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 disutility as per Grade 3 for clinically identified AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA866	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA405	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post EAG clarification queries analyses									
EAG QB1. Independent curves OS - gen gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB1. Independent curves OS - log normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB1. Independent curves PFS - log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB1. Independent curves OS - log normal; PFS - log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB1. Independent curves OS - gen gamma; PFS - log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB2. Random effects NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB3. Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and regorafenib (CORRECT) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)
EAG QB3. Digitised trifluridine-tipiracil (pooled RECOURSE and Yoshino et al) and regorafenib (CONCUR) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB3. Digitised trifluridine-tipiracil (TERRA) and regorafenib (CORRECT) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB3. Digitised trifluridine-tipiracil (TERRA) and regorafenib (CONCUR) data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB4. Use FRESCO data only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB4. Use FRESCO-2 data only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB7. Use mean AE duration data from Pooled FRESCO and FRESCO-2 trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB9. Use RDI from respective trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB10. Apply alternative RDI for all treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB11. Subsequent therapy proportions from clinical opinion + 10% of patients receiving subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB12. Subsequent therapy duration: 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB12. Subsequent therapy duration: 4 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: Dominant means costs less and is more effective. AE, adverse event; BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal.

Most of the scenario analyses conducted have little impact on the ICER. Fruquintinib remained dominant vs regorafenib in all the scenarios considered, with regorafenib modelled at list price. In the comparison with BSC, four of the 29 scenarios presented in the company submission and 7 of the 18 scenarios presented in the response to the EAG queries resulted in an increase or decrease in the ICER of more than 10%. For completeness, the company explored all joint parametric model analyses for fruquintinib versus BSC, however some the OS model fits (e.g. exponential and Gompertz) were not plausible, resulting in a relatively large impact on the ICER for all comparators. The scenarios assuming the TTD curve is equivalent to PFS also had a relatively large impact on the ICERs but should be interpreted cautiously given that TTD curves suggest treatment to progression for everyone is not practical.

5.3 Model validation and face validity check

The company reports their methodology of quality assurance of their cost effectiveness analysis in section B.3.15. The company consulted with leading UK clinicians and HE experts at the UK market access advisory board on several topics detailed in section B.3.15.1. The economic model was quality-assured through extensive quality checking processes conducted by the model developers and by four other health economists not involved in the development of the model.

Tappenden and colleagues checklist was used by the EAG to assess the model and several additional face validity checks were conducted.[68] The results of the black-box checks are reported in Table 30. The EAG identified and corrected an error in the formula used to switch between different RDI settings for trifluridine-tipiracil in the economic model. This adjustment did not alter the company base case analysis but impacted on the EAG preferred assumptions. The EAG clinical expert for the assessment agreed that the modelled extrapolations were plausible as the landmark estimates were similar to the observed data.

Table 30 Model validity check

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	The QALYs and LYGs are equivalent across treatment arms when the model is run trifluridine-tipiracil and regorafenib HRs are set to 1 and the HRs for BSC are replaced with those of fruquintinib, and utilities attached to adverse event are removed.
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	No issues identified
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	No issues identified
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	No issues identified

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	No issues identified
Cost estimation	Set intervention costs to 0	ICER is reduced	No issues identified
	Increase intervention cost	ICER is increased	No issues identified
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	No issues identified
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	No issues identified
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	No issues identified
General	Set all treatment-specific parameters	Costs and QALYs equal for all treatments	No issues identified Equalized survival curves lead to equal health outcomes.

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
	equal for all treatment groups		
	Amend value of each individual model parameter	ICER is changed	No issues identified
	Switch all treatment-specific parameter values	QALYs and costs for each option should be switched	A minor typographical error was identified on the model setting to select different options for the RDI inputs. This was corrected by the EAG. Whilst the change does not impact on the company preferred base case assumptions, it does impact on the EAG preferred model assumptions.

Key: HR, hazard ratio; HSUV, health state utility values; ICER, incremental cost-effectiveness ratio; LYGs, life years gained; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life years.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG undertook several scenario analyses to address issues and uncertainties identified in chapter 4. Additional analyses and assumptions incorporated into the company's preferred economic model (supplied post-clarification questions) included:

1) Adapting results presentation tables to include the option of applying different severity weightings directly to QALYs, rather than reporting unweighted QALYs and assessing them against weighted thresholds. This has a subtle but important difference with regards to results interpretation (i.e. assessing against a £51,000 threshold (i.e. £30,000 x 1.7) implies that NICE's threshold value is £30,000 rather than considering a typical range of the ICER where an intervention may be cost-effective (i.e. between £20,000 to £30,000 per QALY gained) typically referred to in the NICE reference case.
2) Including a correction of the company's conducted scenario analyses around relative dose intensity in the model. This adjustment does not impact on the company's preferred base case analysis but does impact on the EAG's preferred analysis.
3) Applying a switch within the model to allow the application of either drug tariff or eMIT prices for concomitant medications.
4) Exploring a range of alternative EAG-preferred assumptions using the functionality already included within the model by the company.

Full justification for all EAG conducted scenarios and EAG preferred assumptions/data inputs are described in Table 31 below.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG.

The impact of the EAG's preferred assumptions on the ICER is reported in Tables 32 (fully incremental analysis), Table 33 (pairwise analyses, no severity weighting) and Table 34 (pairwise analyses, with a severity weighting of 1.7 applied). Figures 7 and 8 show the EAG preferred probabilistic results using cost-effectiveness acceptability curves and scatter plots of the cost effectiveness plane respectively. The EAG is satisfied that the severity weighting of 1.7 is appropriate for this assessment.

Table 31 Description and justification of EAG's preferred scenario analyses

Scenario number	Parameter or assumption	Company base case	EAG scenario	Justification	Section of EAG report
1	Fruquintinib & BSC OS and PFS parametric survival curves.	Obtained from joint survival models.	Fitted independently to each arm. Fruquintinib (log-normal for OS and PFS); BSC (log-normal for OS and log-logistic for PFS).	There is some uncertainty regarding whether the proportional hazards assumption is satisfied, particularly for PFS. It is also noted that, for BSC, independently fitted extrapolations give better fit to the observed KM data for OS.	4.2.6
2	Regorafenib and trifluridine-tipiracil OS and PFS.	Obtained by applying HRs from a fixed-effects NMA.	Obtained by fitting independent curves to digitised KM data for regorafenib from the CORRECT study)[48] and for trifluridine-tipiracil from the pooled RECOURSE[53] and Yoshino studies.[69]	Applying a hazard ratio directly to an accelerated failure time model (fruquintinib log-normal or generalised gamma) may over or underestimate OS and PFS at different points on the curve. The EAG's clinical expert considered the study populations across CORRECT,[48] FRESCO,[29] RECOURSE[53] and Yoshino[69] to be sufficiently comparable to allow a naïve comparison between studies and fit independent OS and PFS.	4.2.6
3	Scenarios 1 & 2 combined				4.2.6
4	Fruquintinib TTD curve	Log normal curve applied	Generalised gamma curve applied	The EAG notes that both the log-logistic and generalised gamma curves provide a better fit to the KM data (AIC / BIC). Whilst the company model	4.2.6

Scenario number	Parameter or assumption	Company base case	EAG scenario	Justification	Section of EAG report
				caps TTD at PFS, the EAG prefers the generalised gamma curve because it minimises the potential overlap in the PFS and TTD curves at the tail and ensures more clinically plausible outputs, with a lower proportion on treatment at 2 years.	
5.	Regorafenib and trifluridine-tipiracil TTD curves	Applied PFS HRs from the fixed effects NMA for fruquintinib vs regorafenib and versus trifluridine-tipiracil	Use median time on treatment as reported in the regorafenib (CORRECT)[48] and trifluridine-tipiracil (pooled RECOURSE[53] and Yoshino)[69] studies.	The application of PFS HRs to TTD curves to estimate treatment discontinuation assumes that the hazards of treatment discontinuation follow a similar pattern to PFS, and that they are constant over time. This is unlikely to be the case because different treatments are likely to have different adverse event profiles, particularly regorafenib which may have higher initial treatment discontinuation rates than other comparators due to toxicity concerns	4.2.6
6	Scenarios 4 & 5 combined.				
7	RDI assumptions	Apply same RDI, [redacted]% (based on	Treatment specific RDIs based on key clinical trials for fruquintinib (RDI=89.6%,	The EAG's approach more accurately reflects the treatment specific RDI and maintains consistency	4.2.8

Scenario number	Parameter or assumption	Company base case	EAG scenario	Justification	Section of EAG report
		pooled FRESCO and FRESCO-2 studies for Fruquintinib)[29, 34] to all treatments	pooled FRESCO and FRESCO-2 studies),[29, 34] regorafenib (RDI=78.9%, CORRECT trial)[48] and trifluridine-tipiracil (RDI=89.0%, RECOURSE trial)[53]	with the EAG's preferred data source for OS, PFS and ToT.	
8	Concomitant treatment unit costs	DTP costs from the BNF	eMIT prices	eMIT prices are more appropriate for prescription in primary care. The EAG's clinical expert opinion is that most concomitant treatments would be prescribed from primary care for people with mCRC at this stage of their disease.	4.2.8
9	Regorafenib treatment management resource use	Medical oncologist outpatient visit, once every 4 weeks	As per company base case, plus 2 additional medical oncologist visits for regorafenib.	Clinical input to the EAG confirmed that more frequent monitoring is required at the start of treatment, particularly for regorafenib treated patients, to allow for dose adjustments and liver function monitoring	4.2.8
10	Subsequent treatments	Informed by the pooled	Distribution of post progression treatment based on	Aligning subsequent treatment with the efficacy data resulted in some treatments being included that	4.2.8

Scenario number	Parameter or assumption	Company base case	EAG scenario	Justification	Section of EAG report
		FRESCO[29] and FRESCO-2[34] studies to align with the efficacy data	clinical expert opinion sought by the company	are not recommended by NICE (eg bevacizumab). An alternative scenario analysis based on proportions estimated by clinical experts was considered more reflective of practice.	
11	Duration of subsequent treatments	One week	Eight weeks	8-week treatment duration is equivalent to approximately two treatment cycles with chemotherapy, which the EAG's clinical expert considers more appropriate to the use of treatments in UK clinical practice	4.2.8
12	Scenarios 10 & 11 combined				4.2.8
13	**EAG preferred base case (Scenarios 3, 6, 7, 8, 9 & 12 combined)**				

Key: AIC, Akaike information criteria; BIC, Bayesian Information criteria; BNF, British national formulary; BSC, best supportive care; DTP, drug tariff price; eMIT, drugs and pharmaceuticals electronic marketing information tool; HR, hazard ratio; KM, Kaplan-meier; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; RDI. Relative dose intensity; TOT, time on treatment; TTD, time to treatment discontinuation.

Table 32 Fully incremental deterministic analyses, applying EAG scenarios and preferred base case assumptions.

Intervention	Total Costs £	Total Lys	Total QALYs	Incremental Cost	Incremental QALY 1.0	Incremental QALY 1.2	Incremental QALY 1.7	ICER 1.0	ICER 1.2	ICER 1.7
0. Company preferred base case results										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
1. Apply independently fitted curves to fruquintinib (OS: Log normal; PFS: Log normal) and BSC (OS: Log normal); PFS: Log logistic)										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
2. Apply independently fitted OS and PFS curves to regorafenib (CORRECT study; OS: Generalised gamma; PFS: Log-normal); trifluridine-tipiracil (pooled RECOURSE and Yoshino studies; OS: Generalised gamma; PFS: Log-normal)										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
3. Scenarios 1 & 2 combined (All independently fitted OS and PFS curves)										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									

Intervention	Total Costs £	Total Lys	Total QALYs	Incremental Cost	Incremental QALY 1.0	Incremental QALY 1.2	Incremental QALY 1.7	ICER 1.0	ICER 1.2	ICER 1.7
4. Fruquintinib TTD curve (Generalised gamma)										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
5. TTD curves based on median time on treatment for regorafenib (CORRECT study)[48] & trifluridine-tipiracil (pooled RECOURSE and Yoshino studies)[53, 69]										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
6. Scenarios 4 & 5 combined (EAG preferred TTD assumptions)										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
7. Trial specific RDIs applied to each comparator										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									

Intervention	Total Costs £	Total Lys	Total QALYs	Incremental Cost	Incremental QALY 1.0	Incremental QALY 1.2	Incremental QALY 1.7	ICER 1.0	ICER 1.2	ICER 1.7
8. Apply eMIT prices for concomitant treatments										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
9. Apply additional monitoring costs for regorafenib (2 x medical oncologist visits) to monitor potential toxicity										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
10. Subsequent treatments based on company sought clinical expert opinion										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
11. Duration of subsequent treatments: 8-weeks (equivalent to 2 chemotherapy cycles)										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									

Intervention	Total Costs £	Total Lys	Total QALYs	Incremental Cost	Incremental QALY 1.0	Incremental QALY 1.2	Incremental QALY 1.7	ICER 1.0	ICER 1.2	ICER 1.7
12. 10 & 11 combined										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
13. EAG preferred base case deterministic analysis (Scenarios 3, 6, 7, 8, 9 & 12 combined)										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
EAG preferred base case probabilistic analysis (Scenarios 3, 6, 7, 8, 9 & 12 combined)										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									
Additional scenario analyses applied to the EAG preferred deterministic base case (analysis 13 above)										
Use FRESCO study data for clinical inputs										
BSC	[redacted]									
Regorafenib	[redacted]									
Trifluridine/tipiracil	[redacted]									
Fruquintinib	[redacted]									

Intervention	Total Costs £	Total Lys	Total QALYs	Incremental Cost	Incremental QALY 1.0	Incremental QALY 1.2	Incremental QALY 1.7	ICER 1.0	ICER 1.2	ICER 1.7
Use FRESCO-2 study data for clinical inputs										
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine/tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; eMIT, drugs and pharmaceuticals electronic marketing information tool; LY, life years; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; RDI. Relative dose intensity; TTD, time to treatment discontinuation.

Figure 7 EAG preferred cost-effectiveness acceptability curves

Figure 8 EAG preferred cost-effectiveness plane

Table 33 EAG conducted deterministic analyses (pairwise comparisons, QALYs unweighted)

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)
0. Company preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Independently fitted Fruq. and BSC OS /PFS curves	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Independently fitted OS and PFS curves for regorafenib and trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Scenarios 1 & 2 combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Fruquintinib TTD curve (Generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Regorafenib and trifluridine-tipiracil TTD curves based on median time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Scenarios 4 & 5 combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Trial specific RDIs applied to each comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Apply eMIT prices for concomitant treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Apply additional monitoring costs for regorafenib (2 x medical oncologist visits)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Subsequent treatments based on company sought clinical expert opinion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)
11. Duration of subsequent treatments (8 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12. Scenarios 10 & 11 combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13. EAG preferred base case analysis (Scenarios 3, 6, 7, 8, 9 & 12 combined)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14. EAG base case with FRESCO clinical data only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15. EAG base case with FRESCO-2 clinical data only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; eMIT, drugs and pharmaceuticals electronic marketing information tool; LY, life years; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; RDI. Relative dose intensity; TTD, time to treatment discontinuation.

Table 34 EAG conducted deterministic analyses (pairwise comparisons, QALY severity weighting = 1.7)

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)
0. Company preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Independently fitted Fruq and BSC OS / PFS curves	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Independently fitted OS and PFS curves for regorafenib and trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Scenarios 1 & 2 combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Fruquintinib TTD curve (Generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Regorafenib and trifluridine-tipiracil TTD curves based on median time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Scenarios 4 & 5 combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Trial specific RDIs applied to each comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Apply eMIT prices for concomitant treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Apply additional monitoring costs for regorafenib (2 x medical oncologist visits)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Subsequent treatments based on company sought clinical expert opinion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	ICER versus regorafenib			ICER versus trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)
11. Duration of subsequent treatments (8 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12. Scenarios 10 & 11 combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13. EAG preferred base case analysis (Scenarios 3, 6, 7, 8, 9 & 12 combined)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14. EAG base case with FRESCO clinical data only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15. EAG base case with FRESCO-2 clinical data only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; eMIT, drugs and pharmaceuticals electronic marketing information tool; LY, life years; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; RDI. Relative dose intensity; TTD, time to treatment discontinuation.

6.3 Conclusions of the cost effectiveness section

The company submission and economic model provides a robust assessment of the cost-effectiveness of fruquintinib vs. comparators. Whilst there are several uncertainties with regards to most appropriate data sources, and assumptions, these are all fully explored in scenario and sensitivity analyses. The EAG and company preferred assumptions differ with respect to whether hazard ratios or independently fitted survival curves should be used to extrapolate OS and PFS in the model. Whilst the EAG's preferred OS / PFS assumptions favour fruquintinib in the comparison vs. regorafenib and trifluridine-tipiracil, they favour BSC for the comparison of fruquintinib vs. BSC. The EAG also prefers to use trial specific data to inform time on treatment and relative dose intensity in the model. This assumption favours the comparators as it reduces the treatment acquisition costs of regorafenib and trifluridine-tipiracil. A final judgement on cost-effectiveness requires deliberation on these key parameters and uncertainties. The company seek assessment of cost-effectiveness based on a QALY severity weighting of 1.7 and the EAG consider this to be appropriate. Whilst ICERs reported in this document may be useful for decision making, it should be noted that confidential prices exist for comparator treatments. ICERs with these confidential prices applied are supplied in a separate confidential appendix for the committee's consideration.

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8 Appendices

Table 35 Summary of baseline demographics and disease characteristics – FRESCO and FRESCO-2, ITT population, CORRECT, RECOURSE and Yoshino 2012, Xu 2017, CONCUR and TERRA studies [adapted from Table 7, Document B of the CS]

Category	FRESCO*		FRESCO-2*		CORRECT*		RECOURSE*		Yoshino 2012*	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Regorafenib N=505	Placebo N=255	Trifluridine / tipiracil N=534	Placebo N=266	Trifluridine/ tipiracil N=112	Placebo N=57
Age, years										
Mean (SD)	54.3 (10.70)	55.1 (10.53)	62.2 (10.41)	62.4 (9.67)	Median (IQR) 61 (54.0, 67.0)	Median (IQR) 61 (54.0, 68.0)	Median (range) 63 (27-82)	Median (range) 63 (27-82)	Median (range) 63 (28-80)	Median (range) 62 (39-79)
Sex, n (%)										
Female	120 (43.2)	41 (29.7)	216 (46.9)	90 (39.1)	194 (38.4)	102 (40.0)	208 (39)	101 (38)	48 (43)	29 (51)
Male	158 (56.8)	97 (70.3)	245 (53.1)	140 (60.9)	311 (62.0)	153 (60.0)	326 (61)	165 (62)	64 (57)	28 (49)
Race, n (%)										
American Indian or Alaska native	0	0	0	1 (0.4)	NR	NR	NR	NR	NR	NR
Asian	278 (100)	138 (100)	43 (9.3)	18 (7.8)	76 (15)	35 (14)	184 (34)	94 (35)	NR	NR
Black or African American	0	0	13 (2.8)	7 (3.0)	6 (1)	8 (3)	4 (<1)	5 (2)	NR	NR
Native Hawaiian or other Pacific Islander	0	0	3 (0.7)	2 (0.9)	NR	NR	NR	NR	NR	NR
White	0	0	367 (79.6)	192 (83.5)	392 (78)	201 (79)	306 (57)	155 (58)	NR	NR
Other	0	0	5 (1.1)	2 (0.9)	NR	NR	NR	NR	NR	NR
Multiple races	0	0	2 (0.4)	0	NR	NR	NR	NR	NR	NR
Not reported/unknown	0	0	28 (6.1)	8 (3.5)	31 (6)	11 (4)	NR	NR	NR	NR
Ethnicity, n (%)										
Han Chinese	272 (97.8)	135 (97.8)	0	0	NR	NR	NR	NR	NR	NR

Category	FRESCO*		FRESCO-2*		CORRECT*		RECOURSE*		Yoshino 2012*	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Regorafenib N=505	Placebo N=255	Trifluridine / tipiracil N=534	Placebo N=266	Trifluridine/ tipiracil N=112	Placebo N=57
Non-Han Chinese	6 (2.2)	3 (2.2)	0	0	NR	NR	NR	NR	NR	NR
Hispanic or Latino	0	0	20 (4.3)	14 (6.1)	NR	NR	NR	NR	NR	NR
Not Hispanic or Latino	0	0	405 (87.9)	202 (87.8)	NR	NR	NR	NR	NR	NR
Not reported/unknown	0	0	36 (7.8)	14 (6.1)	NR	NR	NR	NR	NR	NR
Region and Country, n (%)										
China	278 (100)	138 (100)	0	0	NR	NR	NR	NR	NR	NR
North America	0	0	82 (17.8)	42 (18.3)	NR	NR	NR	NR	NR	NR
Europe	0	0	329 (71.4)	166 (72.2)	NR	NR	NR	NR	NR	NR
Asia Pacific (Japan and Australia)	0	0	50 (10.8)	22 (9.6)	NR	NR	NR	NR	NR	NR
Japan	NR	NR	NR	NR	NR	NR	178 (33)	88 (33)	112 (100)	57 (100)
United States, Europe, Australia	NR	NR	NR	NR	NR	NR	356 (67)	178 (67)	NR	NR
North America, western Europe, Israel, Australia	NR	NR	NR	NR	420 (83)	212 (83)	NR	NR	NR	NR
Asia	NR	NR	NR	NR	69 (14)	35 (14)	NR	NR	NR	NR
Eastern Europe	NR	NR	NR	NR	16 (3)	8 (3)	NR	NR	NR	NR
BMI (kg/m^2)										
n	278	138	450	225	NR	NR	NR	NR	NR	NR
Mean (SD)	23.19 (3.286)	23.52 (3.429)	26.00 (5.159)	25.77 (5.218)	NR	NR	NR	NR	NR	NR
ECOG PS, n (%)										
0	77 (27.7)	37 (26.8)	196 (42.5)	102 (44.3)	265 (52)	146 (57)	301 (56)	147 (55)	72 (64)	35 (61)
1	201 (72.3)	101 (73.2)	265 (57.5)	128 (55.7)	240 (48)	109 (43)	233 (44)	119 (45)	37 (33)	21 (37)
2	0	0	0	0	0	0	0	0	3 (3)	1 (2)
Time since first diagnosis of CRC (months)										
n	277[†]	138	461	230	NR	NR	NR	NR	NR	NR

Category	FRESCO*		FRESCO-2*		CORRECT*		RECOURSE*		Yoshino 2012*	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Regorafenib N=505	Placebo N=255	Trifluridine / tipiracil N=534	Placebo N=266	Trifluridine/ tipiracil N=112	Placebo N=57
Mean (SD)	2.24 (1.548)	2.43 (1.788)	52.74 (30.406)	56.02 (28.846)	NR	NR	NR	NR	NR	NR
Median	1.79	2.04	47.18	49.38	NR	NR	NR	NR	NR	NR
Min, max	0.1, 9.7	0.3, 9.8	6.0, 242.4	7.1, 154.4	NR	NR	NR	NR	NR	NR
Stage of CRC at first diagnosis, n (%)										
Stage I	8 (2.9)	4 (2.9)	20 (4.3)	6 (2.6)	NR	NR	NR	NR	NR	NR
Stage II	34 (12.2)	18 (13.0)	32 (6.9)	17 (7.4)	NR	NR	NR	NR	NR	NR
Stage III	118 (42.4)	51 (37.0)	139 (30.2)	84 (36.5)	NR	NR	NR	NR	NR	NR
Stage IV	117 (42.1)	63 (45.7)	264 (57.3)	119 (51.7)	NR	NR	NR	NR	NR	NR
Missing	1 (0.4)	2 (1.4)	6 (1.3)	4 (1.7)	NR	NR	NR	NR	NR	NR
Primary site at first diagnosis, n (%)										
Colon	147 (52.9)	70 (50.7)	279 (60.5)	137 (59.6)	323 (64)	172 (68)	338 (63)	161 (61)	63 (56)	36 (63)
Rectum	125 (45.0)	60 (43.5)	143 (31.0)	70 (30.4)	151 (30)	69 (27)	196 (37)	105 (39)	49 (44)	21 (37)
Colon-rectum	6 (2.2)	7 (5.1)	39 (8.5)	23 (10.0)	30 (6)	14 (5)	0	0	0	0
Missing	0	1 (0.7)	0	0	NR	NR	0	0	0	0
Primary tumour location at first diagnosis, n (%)										
Left (splenic flexure, descending/transverse /sigmoid colon and rectum)	214 (77.0)	115 (83.3)	335 (72.7)	162 (70.4)	NR	NR	NR	NR	NR	NR
Right (caecum, ascending colon and hepatic flexure)	56 (20.1)	21 (15.2)	97 (21.0)	53 (23.0)	NR	NR	NR	NR	NR	NR
Left and right	4 (1.4)	0	4 (0.9)	2 (0.9)	NR	NR	NR	NR	NR	NR
Unknown	4 (1.4)	1 (0.7)	25 (5.4)	13 (5.7)	NR	NR	NR	NR	NR	NR
Missing	0	1 (0.7)	0	0	NR	NR	NR	NR	NR	NR
Duration of metastatic disease (months)										
n	278	138	461	230	NR	NR	NR	NR	NR	NR

Category	FRESCO*		FRESCO-2*		CORRECT*		RECOURSE*		Yoshino 2012*	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Regorafenib N=505	Placebo N=255	Trifluridine / tipiracil N=534	Placebo N=266	Trifluridine/ tipiracil N=112	Placebo N=57
Mean (SD)	18.92 (12.946)	20.57 (14.626)	44.01 (23.978)	46.65 (24.607)	NR	NR	NR	NR	NR	NR
Median	16.03	17.22	37.88	40.97	31.0	29.9	NR	NR	NR	NR
Min, max	0.9, 79.0	1.9, 81.6	6.0, 192.8	7.1, 147.1	NR	NR	NR	NR	NR	NR
Categories, n (%)					NR	NR			NR	NR
<18 months‡/≤18 months§	163 (58.6)	75 (54.3)	37 (8.0)	13 (5.7)	91 (18)	49 (19)	111 (21)	55 (21)	NR	NR
≥18 months‡/>18 months§	115 (41.4)	63 (45.7)	424 (92.0)	217 (94.3)	414 (82)	206 (81)	423 (79)	211 (79)	NR	NR
Liver metastases, n (%)										
Yes	185 (66.5)	102 (73.9)	339 (73.5)	156 (67.8)	NR	NR	NR	NR	65 (58)	38 (67)
No	93 (33.5)	36 (26.1)	122 (26.5)	74 (32.2)	NR	NR	NR	NR	47 (42)	19 (33)
***KRAS*‡/*RAS*§ gene status, n (%)**										
Wild type	157 (56.5)	74 (53.6)	170 (36.9)	85 (37.0)	NR	NR	NR	NR	54 (55)	24 (48)
Mutant	121 (43.5)	64 (46.4)	291 (63.1)	145 (63.0)	NR	NR	NR	NR	45 (45)	26 (52)
No KRAS mutation	NR	NR	NR	NR	205 (41)	94 (37)	262 (49)	131 (49)	NR	NR
KRAS mutation	NR	NR	NR	NR	273 (54)	157 (52)	272 (51)	135 (51)	NR	NR
***BRAF*§ gene status, n (%)**										
Wild type	NR	NR	401 (87.0)	198 (86.1)	NR	NR	NR	NR	NR	NR
V600E mutation	NR	NR	7 (1.5)	10 (4.3)	NR	NR	NR	NR	NR	NR
Other mutation	NR	NR	53 (11.5)	22 (9.6)	NR	NR	NR	NR	NR	NR
No BRAF mutation	NR	NR	NR	NR	322/336 (96)	163/166 (98)	NR	NR	NR	NR
BRAF mutation	NR	NR	NR	NR	14/336 (4)	3/166 (2)	NR	NR	NR	NR
Microsatellite/Mismatch repair status, n (%)										
MSS and/or pMMR	NR	NR	427 (92.6)	215 (93.5)	NR	NR	NR	NR	NR	NR
MSI-H and/or dMMR	NR	NR	5 (1.1)	4 (1.7)	NR	NR	NR	NR	NR	NR
Unknown	NR	NR	29 (6.3)	11 (4.8)	NR	NR	NR	NR	NR	NR

Category	FRESCO*		FRESCO-2*		CORRECT*		RECOURSE*		Yoshino 2012*	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Regorafenib N=505	Placebo N=255	Trifluridine / tipiracil N=534	Placebo N=266	Trifluridine/ tipiracil N=112	Placebo N=57
Prior use of VEGF inhibitor, n (%)										
Yes	84 (30.2)	41 (29.7)	445 (96.5)	221 (96.1)	NR	NR	NR	NR	NR	NR
No	194 (69.8)	97 (70.3)	16 (3.5)	9 (3.9)	NR	NR	NR	NR	NR	NR
Prior use of EGFR inhibitor, n (%)										
Yes	40 (14.4)	19 (13.8)	180 (39.0)	88 (38.3)	NR	NR	NR	NR	NR	NR
No	238 (85.6)	119 (86.2)	281 (61.0)	142 (61.7)	NR	NR	NR	NR	NR	NR
Prior treatment with EGFR/VEGF inhibitors, n (%)										
No anti-VEGF and no anti-EGFR	167 (60.1)	83 (60.1)	4 (0.9)	5 (2.2)	NR	NR	NR	NR	NR	NR
Anti-VEGF, anti-EGFR or both	111 (39.9)	55 (39.9)	457 (99.1)	225 (97.8)	NR	NR	NR	NR	NR	NR
Anti-VEGF and no anti-EGFR	71 (25.5)	36 (26.1)	277 (60.1)	137 (59.6)	NR	NR	NR	NR	NR	NR
Anti-EGFR and no anti-VEGF	27 (9.7)	14 (10.1)	12 (2.6)	4 (1.7)	NR	NR	NR	NR	NR	NR
Both anti-VEGF and anti-EGFR	13 (4.7)	5 (3.6)	168 (36.4)	84 (36.5)	NR	NR	NR	NR	NR	NR
Prior treatment with trifluridine-tipiracil and/or regorafenib, n (%)[§]										
Trifluridine-tipiracil	0	0	240 (52.1)	121 (52.6)	NR	NR	NR	NR	NR	NR
Regorafenib	0	0	40 (8.7)	18 (7.8)	NR	NR	91 (17)	53 (20)	NR	NR
Trifluridine-tipiracil and regorafenib	0	0	181 (39.3)	91 (39.6)	NR	NR	NR	NR	NR	NR
Number of prior treatment lines										
Median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	NR	NR	NR	NR	NR	NR
2 or 3, n (%)	190 (68.3)	98 (71.0)	77 (16.7)	44 (19.1)	NR	NR	214 (40)	99 (37)	NR	NR
>3, n (%)	88 (31.7)	40 (29.0)	384 (83.3)	186 (80.9)	NR	NR	320 (60)	167 (63)	NR	NR

Category	FRESCO*		FRESCO-2*		CORRECT*		RECOURSE*		Yoshino 2012*	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230	Regorafenib N=505	Placebo N=255	Trifluridine / tipiracil N=534	Placebo N=266	Trifluridine/ tipiracil N=112	Placebo N=57
Number of prior treatment lines for metastatic disease, n (%)										
≤3	221 (79.5)	107 (77.5)	125 (27.1)	64 (27.8)	NR	NR	NR	NR	NR	NR
>3	57 (20.5)	31 (22.5)	336 (72.9)	166 (72.2)	NR	NR	NR	NR	NR	NR
1-2	NR	NR	NR	NR	135 (27)	63 (25)	NR	NR	NR	NR
3	NR	NR	NR	NR	125 (25)	72 (28)	NR	NR	NR	NR
≥4	NR	NR	NR	NR	245 (49)	120 (47)	NR	NR	NR	NR

Table 35 (Continued)

Category	Xu 2017		CONCUR		TERRA	
	Fruquintinib + BSC N=47	Placebo + BSC N=24	Regorafenib + BSC N=136	Placebo + BSC N=68	Trifluridine-tipiracil +BSC N=271	Placebo + BSC N=135
Age, years						
Mean (SD)	Median (range) 50.0 (25.0, 69.0)	Median (range) 54.0 (38.0, 70.0)	Median (IQR) 57.5 (50.0, 66.0)	Median (IQR) 55.5 (48.5, 62.0)	Median (range) 58 (26, 81)	Median (range) 56 (24, 80)
Sex, n (%)						
Female	12 (25.5)	7 (29.2)	51 (38)	35 (51)	101 (37)	51 (38)
Male	35 (74.5)	17 (70.8)	85 (63)	33 (49)	170 (63)	84 (62)
Race, n (%)						
American Indian or Alaska native	NR	NR	NR	NR	0	0
Asian	NR	NR	NR	NR	271 (100)	135 (100)
Black or African American	NR	NR	NR	NR		
Native Hawaiian or other Pacific Islander	NR	NR	NR	NR	0	0
White	NR	NR	NR	NR	0	0
Other	NR	NR	NR	NR	0	0
Multiple races	NR	NR	NR	NR	0	0
Not reported/unknown	NR	NR	NR	NR	0	0

Category	Xu 2017		CONCUR		TERRA	
	Fruquintinib + BSC N=47	Placebo + BSC N=24	Regorafenib + BSC N=136	Placebo + BSC N=68	Trifluridine-tipiracil +BSC N=271	Placebo + BSC N=135
Ethnicity, n (%)						
Han Chinese	NR	NR	NR	NR	NR	NR
Non-Han Chinese	NR	NR	NR	NR	NR	NR
Hispanic or Latino	NR	NR	NR	NR	NR	NR
Not Hispanic or Latino	NR	NR	NR	NR	NR	NR
Not reported/unknown	NR	NR	NR	NR	NR	NR
Region and Country, n (%)						
China	47 (100)	47 (100)	112 (82)	60 (88)	204 (75)	101 (75)
North America	0	0	0	0	0	0
Europe	0	0	0	0	0	0
Asia Pacific (Japan and Australia)	0	0	0	0	0	0
Japan	0	0	0	0	0	0
United States, Europe, Australia	0	0	0	0	0	0
North America, western Europe, Israel, Australia	0	0	0	0	0	0
Asia	0	0	24 (18)	8 (12)	0	0
Eastern Europe	0	0	0	0	0	0
Republic of Korea	0	0	0	0	55 (20)	26 (19)
Thailand	0	0	0	0	12 (4)	8 (6)
BMI (kg/m^2)						
n	NR	NR	NR	NR	NR	NR
Mean (SD)	NR	NR	Median (IQR) 23.1 (20.8, 25.5)	22.8 (20.0, 25.0)	Median (range) 23.4 (15.8, 36.1)	Median (range) 23.0 12.9, 31.6)
ECOG PS, n (%)						
0	6 (12.8)	5 (20.8)	35 (26)	15 (22)	64 (24)	30 (22)
1	41 (87.2)	19 (79.2)	101 (74)	53 (78)	207 (76)	105 (78)
2	0	0	0	0	0	0
Time since first diagnosis of CRC (months)						
n	NR	NR	NR	NR	NR	NR
Mean (SD)	NR	NR	NR	NR	NR	NR

Category	Xu 2017		CONCUR		TERRA	
	Fruquintinib + BSC N=47	Placebo + BSC N=24	Regorafenib + BSC N=136	Placebo + BSC N=68	Trifluridine-tipiracil +BSC N=271	Placebo + BSC N=135
Median	NR	NR	NR	NR	22.8	26.3
Min, max	NR	NR	NR	NR	NR	NR
Stage of CRC at first diagnosis, n (%)						
Stage I	NR	NR	NR	NR	NR	NR
Stage II	NR	NR	NR	NR	NR	NR
Stage III	NR	NR	NR	NR	NR	NR
Stage IV	NR	NR	NR	NR	NR	NR
Missing	NR	NR	NR	NR	NR	NR
Primary site at first diagnosis, n (%)						
Colon	24 (51.1)	13 (54.2)	79 (58)	48 (71)	154 (57)	85 (63)
Rectum	23 (48.9)	11 (45.8)	53 (39)	19 (28)	117 (43)	50 (37)
Colon-rectum	0	0	4 (3)	1 (1)	0	0
Missing	0	0	0	0	0	0
Primary tumour location at first diagnosis, n (%)						
Left (splenic flexure, descending/transverse /sigmoid colon and rectum)	NR	NR	NR	NR	NR	NR
Right (caecum, ascending colon and hepatic flexure)	NR	NR	NR	NR	NR	NR
Left and right	NR	NR	NR	NR	NR	NR
Unknown	NR	NR	NR	NR	NR	NR
Missing	NR	NR	NR	NR	NR	NR
Duration of metastatic disease (months)						
n	NR	NR	NR	NR	NR	NR
Mean (SD)	NR	NR	NR	NR	NR	NR
Median	NR	NR	20.3	19.9	18.6	23.3
Min, max	NR	NR	NR	NR	NR	NR
Categories, n (%)	NR	NR	NR	NR	NR	NR
<18 months/≤18 months	20 (42.6)	14 (58.3)	53 (39)	32 (47)	134 (49)	52 (39)
≥18 months/>18 months	27 (57.4)	10 (41.7)	83 (61)	36 (53)	137 (51)	83 (61)

Category	Xu 2017		CONCUR		TERRA	
	Fruquintinib + BSC N=47	Placebo + BSC N=24	Regorafenib + BSC N=136	Placebo + BSC N=68	Trifluridine-tipiracil +BSC N=271	Placebo + BSC N=135
Liver metastases, n (%)						
Yes	29 (61.7)	17 (70.8)	NR	NR	NR	NR
No	18 (38.3)	7 (29.2)	NR	NR	NR	NR
***KRAS/RAS* gene status, n (%)**						
Wild type	NR	NR	0	0	172 (63)	85 (63)
Mutant	NR	NR	0	0	99 (37)	50 (37)
No KRAS mutation	NR	NR	50 (37)	29 (43)	NR	NR
KRAS mutation	NR	NR	46 (34)	18 (26)	NR	NR
Unknown	NR	NR	40 (29)	21 (31)	NR	NR
***BRAF* gene status, n (%)**						
Wild type	NR	NR	NR	NR	NR	NR
V600E mutation	NR	NR	NR	NR	NR	NR
Other mutation	NR	NR	NR	NR	NR	NR
No BRAF mutation	NR	NR	28 (21)	14 (21)	NR	NR
BRAF mutation	NR	NR	0	1 (1)	NR	NR
Unknown	NR	NR	108 (79)	53 (78)	NR	NR
Microsatellite/Mismatch repair status, n (%)						
MSS and/or pMMR	NR	NR	NR	NR	NR	NR
MSI-H and/or dMMR	NR	NR	NR	NR	NR	NR
Unknown	NR	NR	NR	NR	NR	NR
Prior use of VEGF inhibitor, n (%)						
Yes	15 (31.9)	7 (29.2)	NR	NR	NR	NR
No	29 (61.7)	17 (70.8)	NR	NR	NR	NR
Unknown	3 (6.4)	0	NR	NR	NR	NR
Prior use of EGFR inhibitor, n (%)						
Yes	NR	NR	NR	NR	NR	NR
No	NR	NR	NR	NR	NR	NR
Prior treatment with EGFR/VEGF inhibitors, n (%)						
No anti-VEGF and no anti-EGFR	NR	NR	56 (41)	26 (38)	148 (55)	66 (49)
Anti-VEGF, anti-EGFR or both	NR	NR	80 (59)	42 (62)	123 (45)	69 (51)

Category	Xu 2017		CONCUR		TERRA	
	Fruquintinib + BSC N=47	Placebo + BSC N=24	Regorafenib + BSC N=136	Placebo + BSC N=68	Trifluridine-tipiracil +BSC N=271	Placebo + BSC N=135
Anti-VEGF and no anti-EGFR	NR	NR	32 (24)	13 (19)	52 (19)	27 (20)
Anti-EGFR and no anti-VEGF	NR	NR	24 (18)	17 (25)	46 (17)	25 (19)
Both anti-VEGF and anti-EGFR	NR	NR	24 (18)	12 (18)	25 (9)	17 (13)
Prior treatment with trifluridine-tipiracil and/or regorafenib, n (%)						
Trifluridine-tipiracil	NR	NR	NR	NR	NR	NR
Regorafenib	NR	NR	NR	NR	NR	NR
Trifluridine-tipiracil and regorafenib	NR	NR	NR	NR	NR	NR
Number of prior treatment lines, n (%)						
Median (Q1, Q3)	NR	NR	NR	NR	NR	NR
2	12 (25.5)	7 (29.2)	31 (23)	14 (21)	62 (23)	25 (19)
2 or 3	NR	NR	NR	NR	NR	NR
3	NR	NR	32 (24)	19 (28)	74 (27)	36 (27)
>3	NR	NR	NR	NR	NR	NR
≥3	35 (74.5)	17 (70.8)	NR	NR	NR	NR
≥4	NR	NR	73 (54)	35 (51)	135 (50)	74 (55)
Number of prior treatment lines for metastatic disease, n (%)						
≤3	NR	NR	NR	NR	NR	NR
>3	17 (36.2)	7 (29.2)	NR	NR	NR	NR
1-2	NR	NR	48 (35)	24 (35)	NR	NR
2-3	30 (63.8)	17 (70.8)	NR	NR	NR	NR
3	NR	NR	32 (24)	17 (25)	NR	NR
≥4	NR	NR	52 (38)	27 (40)	NR	NR

Source: FRESCO final CSR (84), FRESCO tables (111), FRESCO-2 final CSR (19), Dasari et al, 2023 (20), Xu 2017, Li 2015, Xu 2018. †Time of first diagnosis was missing for one patient; ‡FRESCO only; §FRESCO-2 only. **Key**: BMI, body mass index; BRAF, v-raf murine sarcoma viral oncogene homologue B; BSC, best supportive care; CSR, clinical study report; CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor; ITT, intention-to-treat; KRAS, Kirsten rat sarcoma viral oncogene homologue; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NR, not reported; pMMR, proficient mismatch repair; Q, quartile; RAS, rat sarcoma virus; SD, standard deviation; VEGF, vascular endothelial growth factor.

Single Technology Appraisal

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 07 May 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Points of clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 1.1, Page xv EAG report, Section 1.5, Pages xvii, xix EAG report, Section 3.6, Page 32 EAG report, Section 4.2.6, Pages 46, 47, 48 (Table 15) EAG report, Section 6.2, Page 84	Change from: "FRESCO studies" or "FRESCO trials" To: **"pooled** FRESCO **and FRESCO-2** studies"	The EAG report is currently inconsistent in the way the pooled FRESCO and FRESCO-2 data is referred to. The change is proposed to ensure consistency and clarity throughout the EAG report, and avoid confusion between the pooled data and individual FRESCO study.	Text amended as requested.
	Change from: "FRESCO trials" To: **"pooled** FRESCO **and FRESCO-2** trials"		Text amended as requested.
	Change from: *"FRESCO – pooled (ind. curves)"* To: "***Pooled data*** *(ind. curves)"*		Text amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 1.2, Page xvi	Change from: "*Overall, the technology is modelled to affect QALYs by:* • *Increasing overall survival compared to other treatments and best supportive care (BSC)* • *Increasing the amount of time patients remain progression free, leading to improvements in quality of life."* To: "*Overall, the technology is modelled to affect QALYs by:* • *Increasing overall survival compared to other treatments and best supportive care (BSC)* • *Increasing the amount of time patients remain progression free, leading to improvements in quality of life* • ***Improving the toxicity profile compared to regorafenib and trifluridine-tipiracil***"	The current statement does not fully reflect the reasons for a QALY gain in the analysis; specifically, the company would like to highlight that fruquintinib also affects QALYs through an improved toxicity profile when compared to regorafenib and trifluridine-tipiracil.	Not a factual accuracy. However, the text is updated for completeness, also noting that the impact on adverse events on QALYs in the model is minor.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 1.2, Page xvi	Change from: "Overall, the technology is modelled to affect costs by: • Leading to similar treatment acquisition costs to regorafenib (list price) but increasing treatment costs compared to trifluridine-tipiracil at list price and compared to BSC. • Increasing disease management costs, due to longer time spent progression free." To: "Overall, the technology is modelled to affect costs by: • Leading to similar treatment acquisition costs to regorafenib (list price) but increasing treatment costs compared to trifluridine-tipiracil at list price and compared to BSC. • Increasing disease management costs, due to longer time spent progression free • **Reducing costs associated with treatment related TEAEs, due to an**	The current statement does not fully reflect the cost differences in the model for fruquintinib vs. other treatments; specifically, the company would like to highlight that fruquintinib also reduces costs through an improved toxicity profile when compared to regorafenib and trifluridine-tipiracil.	Not a factual accuracy. However, the text is updated for completeness, also noting that the impact on adverse events on QALYs in the model is minor.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	improved toxicity profile compared to regorafenib and trifluridine-tipiracil."		
EAG report, Section 3.2.1, Page 12	The EAG report states: "*Thus, the EAG's clinical expert considers that participants in FRESCO-2 may be less likely than those in FRESCO to benefit from treatment.*" The company accept that this is clinical opinion but would like to highlight that the clinical trial data demonstrate that the relative effect of fruquintinib vs placebo is the same in both trials (FRESCO and FRESCO-2).	While the current statement reflects clinical opinion, the relative effects for OS and PFS are very similar across the FRESCO and FRESCO-2 clinical trials: • **OS** – FRESCO: HR = 0.65 (95% CI: 0.51, 0.83; p<0.001) (CS, Table 11, page 60) – FRESCO-2: HR = 0.66 (95% CI: 0.55, 0.80; p<0.001) (CS, Table 11, page 60) • **PFS** – FRESCO: HR = 0.26 (95% CI: 0.21, 0.34; p<0.001) (CS, Table 12, page 62) – FRESCO-2: HR = 0.32 (95% CI: 0.27, 0.39; p<0.001) (CS, Table 12, page 62)	Thank you for your comment. No amendment required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report Section 3.2.2, Page 22	Change from: "Across both trials, a total of 84.8% of fruquintinib participants and 91.8% of placebo participants experienced PD or death. Median PFS was 3.7 months and 1.8 months, respectively, HR 0.31 (95%CI 0.27, 0.36)." To: "**In the pooled analysis of FRESCO and FRESCO-2,** a total of 84.8% of fruquintinib participants and 91.8% of placebo participants experienced PD or death**, and m**edian PFS was 3.7 months and 1.8 months, respectively, HR 0.31 (95%CI 0.27, 0.36)."	In the current statement it is not clear that median PFS data are from the pooled analysis of FRESCO and FRESCO-2.	Text amended as requested.
EAG report, Section 3.2.4, Page 27 and Table 10 (Page 26)	Reporting of TEAEs leading to death for both FRESCO and FRESCO-2 trials: No amendment proposed but clarification is provided under "Justification for amendment"	No amendment required; however, the company wish to confirm that: For the FRESCO trial: • The data for TEAEs leading to death should be as highlighted by the EAG and as reported in Table 2 of the Li et al, 2018 (1), publication: 9/278 (3.2%) in the fruquintinib arm and 2/137	Thank you for clarifying these points. We have updated Table 10 of the EAG report and removed the related text describing the discrepancies.

		(1.5%) in the placebo arm (see also Table 18 [page 100] of the FRESCO CSR (2)). • The company would like to clarify that the data reported in the CS (Document B), Table 23 (page 101) for TEAEs leading to death of 4/278 (1.4%) in the fruquintinib arm and 0/137 in the placebo arm **were treatment-related** TEAEs leading to death (see also Table 18 [page 100] of the FRESCO CSR (2)). For the FRESCO-2 trial: • The reason for the discrepancy highlighted in the data reported for TEAEs leading to death in Table 23 of the CS (Document B) and noted by the EAG is as per the footnote to Table 31 (page 127-129) of the CSR (3) and as described by the EAG on page 27 of the report.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		See **Clarification Table 10**	
EAG report, Section 4.2.5, Page 38	Change from: *"A 15-year time horizon is explored"* To: *"A **5-year time** horizon is also explored in scenario analyses but only has a minimal impact on the ICER ~~because 0% of the cohort are modelled to remain alive after 10 years~~."*	The current statement does not accurately reflect the scenarios explored by the Company. However, the conclusions made by the EAG are correct, and 0% of the cohort are modelled to remain alive after 10 years.	Text amended as requested.
EAG report, Section 4.2.6, Page 44	Change from: "*EAG notes that the RE analysis leads to an increase of about £4,000 in the company's base case ICER."* To: "*EAG notes that the RE analysis leads to an increase of about £4,000 in the company's base case ICER **vs trifluridine-tipiracil**."*	The current statement is not clear that the increase in the ICER is specific to the pairwise comparison with trifluridine-tipiracil.	Text amended as requested.
EAG report, Section 4.2.6, Page 44	Change from: "The company again assumed that the proportional hazards and accelerated failure time assumptions hold true across the different comparators included in the NMA, enabling the direct application of	The current statement does not fully reflect the justification for using the NMA in the Company base case.	Text amended to provide more clarity of the company position. "The company justified their preferred approach

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	HRs. The company preferred this approach to fitting independent curves to digitised KM data from the respective trials because the use of the NMA allowed inclusion of the totality of the evidence." To: "The company again assumed that the proportional hazards and accelerated failure time assumptions hold true across the different comparators included in the NMA, enabling the direct application of HRs. The company preferred this approach to fitting independent curves to digitised KM data from the respective trials because the use of the NMA **fully aligns with the NICE methods guide**, allowed inclusion of the totality of the evidence **while preserving randomisation, and aligns with the approach in TA866**."		on the grounds that the use of the NMA aligns with the NICE methods guide, allows inclusion of the totality of the evidence, preserves randomisation from the trials and aligns with the approach taken for TA886."
EAG report, Section 4.2.6, Page 53	Change from: *"It assumes that the hazards of treatment discontinuation follow a similar pattern to PFS, and that they are constant over time."* To: *"It assumes that the hazard of treatment discontinuation* ***is proportional between***	To estimate TTD for regorafenib and trifluridine-tipiracil, the PFS HR vs fruquintinib for each treatment is applied to the fruquintinib TTD curve. Therefore, there is no assumption made that the shape of the hazard function for TTD is the same as for PFS, as suggested in the EAG report. Rather, the	Text amended as requested

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	***treatments**, and that **the relationship is** constant over time."*	assumption is made that the hazards of treatment discontinuation for regorafenib and trifluridine-tipiracil are proportional to that of fruquintinib TTD.	
EAG report, Section 4.2.7, Page 55	Change from: "The utility values from two of the prior HTAs were used in sensitivity analysis." To: "The **utility decrements associated with progressed disease** from two of the prior HTAs were used in sensitivity analysis."	The current statement does not accurately reflect the model scenario analysis.	Text amended as requested.
EAG report, Section 4.2.7, Page 56	Change from: "…proportions of Grade 1 or 2 TEAEs experience by ≥10% of patients and Grade 3 or above TEAEs experienced by ≥2% of patients, with the disutilities derived from TA866. Most TEAEs were assumed…" To: "…proportions of Grade 1 or 2 **treatment-related** TEAEs experienced by ≥10% of patients and Grade 3 or above **treatment-related** TEAEs experienced by ≥2% of patients, with the disutilities derived from	The current statement is not clear that the model uses treatment-related TEAEs.	Text amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	TA866. Most **treatment-related** TEAEs were assumed…"		
EAG report, Section 4.2.8, Page 59	Change from: "*The costs were estimated based on medication received by ≥ 10% of patients in the pooled FRESCO and FRESCO-2 studies (CS Table 56) combined with the costs per week to give a weighted average cost of £9 per treatment cycle."* To: "*The costs were estimated based on medication received by ≥ 10% of patients in the pooled FRESCO and FRESCO-2 studies (CS Table 56) combined with the costs per week to give a weighted average cost of £9 per treatment cycle* ***in the fruquintinib, regorafenib and trifluridine-tipiracil arms and £8 in the BSC arm****."*	The statement does not accurately reflect the difference in BSC costs between BSC and active treatment arms in the model.	Text amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 4.2.8, Page 60	Change from: "…the proportions derived from the pooled FRESCO and FRESCO-2 trials for fruquitinib were applied to all treatment arms (CS Table 59)" To: "…the proportions derived from the pooled FRESCO and FRESCO-2 trials for fruquintinib were applied to all **active** treatment arms (CS Table 59)"	The statement does not accurately reflect that the model assumes no cost of subsequent treatments in the BSC arm.	Text amended as requested.
EAG report, Section 4.2.8, Page 61	Change from: "*As some concomitant and subsequent treatment medicine costs are available on eMIT, these costs are preferred for use in the model*" To: "*As some concomitant ~~and subsequent treatment~~ medicine costs are available on eMIT, these costs are preferred for use in the model*"	The current statement does not accurately reflect the EAG's preferred base case. Remove the wording indicted in strikethrough in the proposed amendment.	Text amended as requested.
EAG report, Section 4.2.8, Page 61, Table 22	The table does not fully capture the updates to drug costs made by the EAG in their analysis. Please see **Replacement Table 22.**	The current table does not accurately reflect the EAGs preferred base case.	Thank you for noticing this inconsistency which was due to different versions of eMIT prices applied in the report and economic

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			model. Table 22 has been updated accordingly to match the prices used in the economic model. This change has no impact on results.
EAG report, Section 4.2.8, Page 62	Change from: "*An additional outpatient visit in cycle 1 was added in the regorafenib arm in the EAG preferred base case*." To: "***Two** additional outpatient visit**s** in cycle 1 **were** added in the regorafenib arm in the EAG preferred base case."*	The current statement does not accurately reflect the EAGs preferred base case.	Text updated to align with the economic model scenario analysis. Further slight amendment to the text to improve clarity about the justification for the additional scenario carried out.
EAG report, Section 5.1, Page 65	Change from: "*Modelled costs are most sensitive to the treatment acquisition and disease management costs. The rest of the costs (concomitant medicines, adverse reaction management, subsequent treatment and end of life) were similar between the all the interventions"* To: "*Modelled costs are most sensitive to the treatment acquisition, **treatment related TEAE management**, and disease*	The current statement does not reflect that adverse reaction costs are different between fruquintinib and trifluridine-tipiracil; specifically, the company would like to highlight that for the comparison of fruquintinib vs trifluridine-tipiracil, the incremental adverse reaction costs (-£449) are of similar magnitude to incremental disease management costs (£503).	Text amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	management costs. The rest of the costs (concomitant medicines, ~~adverse reaction management,~~ subsequent treatment and end of life) were similar between the all the interventions"		
EAG report, Section 5.2, Page 77	Change from: "The scenarios assuming treatment to progression for trifluridine-tipiracil and regorafenib...". To: "The scenarios assuming the TTD curve is equivalent to the PFS curve"	The current statement does not accurately reflect the scenario analysis conducted.	Text amended as requested.

Issue 2 Factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 1.4, Page xvi	Change from: "To compare the effectiveness of fruquintinib with other relevant comparator treatments (placebo/BSC, trifluridine-tipiracil and regorafenib), the company presents fixed-effects NMAs showing the superiority of fruquintinib for both PFS and OS." To:	To reflect the outputs of the NMA for each comparator and endpoint.	Text amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	"To compare the effectiveness of fruquintinib with other relevant comparator treatments (placebo/BSC, trifluridine-tipiracil and regorafenib), the company presents fixed-effects NMAs**. NMA results showed that fruquintinib was associated with a significant advantage in both OS and PFS vs BSC, a significant advantage in PFS vs regorafenib and trifluridine-tipiracil, and a numerical advantage in OS vs regorafenib and trifluridine-tipiracil.**"		
EAG report, Section 3.3, Page 31	Change from: "*Apart from the situation where no prior anti-VEGF treatment was used, the treatment effects are consistent with those obtained from the NMA*." To: *"**The treatment effects for fruquintinib vs. BSC in all subgroup analyses are consistent with those obtained from the NMA**. Apart from the situation where no prior anti-VEGF treatment was used, the treatment effects **for fruquintinib vs. regorafenib and trifluridine-tipiracil** are consistent with those obtained from the NMA; **however, these data should be interpreted with caution due to the***	The current statement does not reflect the consistent results for fruquintinib vs. BSC, or the limitations associated with the no prior anti-VEGF scenario analyses presented for fruquintinib vs. regorafenib and trifluridine-tipiracil, due to small patient numbers informing the analysis (analysis vs. regorafenib [n/N = 82/204]; analysis vs. trifluridine-tipiracil [n/N = 35/169]).	Text amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	***small patient numbers informing these analyses**."*		

Issue 3 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The spelling of fruquintinib: Page xvii, xx, 37, 43, 44, 60, 63, 65, 78, 82, 83, 84, 92, 94	The company request that the EAG ensure the correct spelling of fruquintinib has been used throughout the report. The company has noted that "*fruquitinib*", "*fruquintinb", "fruquinitinb", and* have been used, and that there are occurrences where a capital "F" has been used for fruquintinib in the middle of a sentence when a lower case "f" should be used.	Correction of spelling	Text amended as requested.
The spelling or presentation of regorafenib: xx, 44, 71, 72, 73, 74, 78, 86, 87, 92, 94,	The company note that there are occurrences where a capital "R" has been used for Regorafenib in the middle of a sentence when a lower case "r" should be used.	Correction of spelling	Text amended as requested.
The spelling or presentation of trifluridine-tipiracil: Pages xx, 33, 34, 44, 53, 65, 71, 72, 73, 74, 75, 76, 83, 92, 94	The company request that the EAG ensure the correct spelling of trifluridine-tipiracil has been used throughout the report. The company has noted that "*tifluridine-tipiracil*" and "*trifluridine tipiracil*" have been used, and that there are occurrences where a capital "T" has been used for trifluridine-	Correction of spelling	Text amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	tipiracil in the middle of a sentence when a lower case “t” should be used.		
EAG report: Section 4.2.6, Page 42	Change from: “*The EAG is satisfied that the decision to use either FRESCO or FRESCO-2 individually, comparted to the pooled data for OS and PFS does not have a major impact on the ICER.”* To: *“The EAG is satisfied that the decision to use either FRESCO or FRESCO-2 individually, **compared** to the pooled data for OS and PFS does not have a major impact on the ICER.”*	Correction of spelling	Text amended as requested.
EAG report, Section 4.2.2, Page 36	Change from: “*MCRC*” To: “*mCRC*”	Correction to ensure consistent abbreviations are used throughout	Text amended as requested.
EAG report, Section 4.2.6, Page 50 (Figure 3)	Change the x-axis label from: “Years” To: “Weeks”	Correction of label	Thank you for identifying this error. Figure label amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 5.1, Page 66 (Table 25)	Correction to QALY shortfall calculations for the Company preferred base case. Please see **Replacement Table 25** for details.	Correction to reporting	QALY shortfalls in the original EAG report were calculated using the McNamara et al. online tool. However, the EAG accepts that the company's calculation is correct and based on more recent data. Table 25 has therefore been updated to ensure consistency. It should be noted that both the original EAG approach and the company approach generate similar conclusions.
EAG report, Section 5.1, Page 67 (Table 26)	Correction to total QALYs in the trifluridine/tipiracil arm, and clarification that total LYs were not reported in the probabilistic analysis. Please see **Replacement Table 26** for details.	Correction to reporting	Thank you for identifying this calculation error in the probabilistic analysis tables for chapter 5. Table amended as requested.
EAG report, Section 5.1, Page 68 (Table 27)	Correction to incremental costs, incremental QALYs and ICERs for the probabilistic analysis results. Correction to the pairwise ICER with the 1.7 QALY weighting applied vs trifluridine-tipiracil for the deterministic analysis. Please see **Replacement Table 27** for details.	Correction to reporting	Thank you for identifying this calculation error in the probabilistic analysis tables for chapter 5. Table amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report, Section 5.2, Page 77	Change from: "In the comparison with BSC, four of the 29 scenarios presented in the company submission and 6 of the 18 scenarios presented in the response to the EAG queries resulted in an increase or decrease in the ICER of more than 10%" To: "In the comparison with BSC, four of the 29 scenarios presented in the company submission and **7** of the 18 scenarios presented in the response to the EAG queries resulted in an increase or decrease in the ICER of more than 10%"	Correction to reporting	Amended as requested
EAG report, Section 6.2, Page 92 Table 33	Correction to the reporting of results for EAG scenarios 14 and 15 with no QALY multiplier applied. Please see **Replacement Table 33.**	Correction to reporting of EAG scenarios	Thank you for noticing this inconsistency which is due mainly to minor rounding errors due to formatting of tables performed by the EAG outside of the model. The table has now been updated so the correct rounding approach is applied.
EAG report, Section 6.2, Page 95, Table 34	Correction to the reporting of results for EAG scenarios 14 and 15 with 1.7 QALY	Correction to reporting of EAG scenarios	Thank you for noticing this inconsistency which is due mainly to minor rounding

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	multiplier applied. Please see **Replacement Table 34.**		errors due to formatting of tables performed by the EAG outside of the model. The table has now been updated so the correct rounding approach is applied.

Issue 4 Errors in confidential mark-up

Location of incorrect marking	Description of incorrect marking	Amended marking	
Note: The company acknowledges that the EAG has utilised the initial company submission (CS) provided on 14 February 2024, predating the revised marking requested by NICE. While certain discrepancies in the confidential markup have been identified, it is important to recognise that the updated marking contained in the documents sent to NICE on 14 March 2024 should serve as the primary reference.			
EAG report, Section 2.3, Page 36	Information linked to anticipated marketing authorisation is confidential.	Change to: "The patient population is defined as *********** ******** ******* ********* ************************ ************** ************** ****************************** *********** ****** *********** ******** *************** *********** *********** ***** * *********** ***** ******** *** ********* *******	Marking updated as requested.

Location of incorrect marking	Description of incorrect marking	Amended marking	
EAG report, Section 1.6, Page xx Table 2 EAG report, Section 5.1, Page 67 Table 26 EAG report, Section 5.1, Page 71 Table 27 EAG report, Section 5.2, Page 74 Table 29 EAG report, Section 5.2, Page 74 Table 32 EAG report, Section 6.2, Page 86 Table 32 EAG report, Section 6.2, Page 92 Table 33 EAG report, Section 6.2, Page 94 Table 34	PAS price ICERs are confidential to prevent back-calculation of the PAS discount.	The company request that the EAG document is updated so the PAS price ICERs are marked as confidential.	Marking updated as requested.

References

Note references cited below can be located in the reference pack provided in the company submission

1. Li J, Qin S, Xu RH, Shen L, Xu J, Bai Y, et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. Jama. 2018;319(24):2486-96.
2. Takeda. 86 FRESCO Clinical Study Report - A randomized, double-blind and placebo-controlled Phase III trial comparing fruquintinib efficacy and safety vs best support care (BSC) in advanced colorectal cancer patients who have failed at least second lines of chemotherapies [Data on file]. London: Takeda; 2017.
3. Takeda. FRESCO-2 Clinical Study Report - A global, multicenter, randomized, placebo-controlled Phase 3 trial to compare the efficacy and safety of fruquintinib plus best supportive care to placebo plus best supportive care in patients with refractory metastatic colorectal cancer [Data on file]. London: Tadeda; 2023.

Supporting information

Note confidential marking on replacement tables in this section reflects the updated marking from March 2024

Clarification Table 10 Overall summary of TEAEs – FRESCO and FRESCO-2, safety sets [reproduced from Table 23, Document B of the CS]

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=137**	**Fruquintinib + BSC N=456**	**Placebo + BSC N=230**
Patients with any TEAE, n (%)	274 (98.6)	121 (88.3)	451 (98.9)	213 (92.6)
CTCAE Grade ≥3	170 (61.2)	27 (19.7)	286 (62.7)	116 (50.4)
Treatment-related	266 (95.7)	97 (70.8)	395 (86.6)	130 (56.5)
Treatment-related CTCAE Grade ≥3	128 (46.0)	10 (7.3)	164 (36.0)	26 (11.3)
Leading to dose reduction	67 (24.1)	6 (4.4)	110 (24.1)	9 (3.9)
Leading to dose interruption	98 (35.3)	14 (10.2)	213 (46.7)	61 (26.5)
Leading to treatment discontinuation	42 (15.1)	8 (5.8)	93 (20.4)	49 (21.3)
Treatment-related leading to dose reduction	61 (21.9)	3 (2.2)	93 (20.4)	7 (3.0)
Treatment-related leading to dose interruption	87 (31.3)	10 (7.3)	134 (29.4)	14 (6.1)
Treatment-related leading to treatment discontinuation	22 (7.9)	1 (0.7)	45 (9.9)	7 (3.0)
TEAE leading to death	**9 (3.2)**	**2 (1.5)**	**49 (10.7)[a]**	**45 (19.6)**
Treatment-related TEAE leading to death	**4 (1.4)**	**0**	**1 (0.4)**	**1 (0.5)**
Patients with any serious TEAE, n (%)	43 (15.5)	8 (5.8)	172 (37.7)	88 (38.3)
CTCAE Grade ≥3	32 (11.5)	7 (5.1)	163 (35.7)	85 (37.0)
Treatment-related	17 (6.1)	2 (1.5)	43 (9.4)	8 (3.5)
Treatment-related CTCAE Grade ≥3	128 (46.0)	10 (7.3)	38 (8.3)	6 (2.6)
Patients with any AESI, n (%)	257 (92.4)	74 (54.0)	368 (80.7)	122 (53.0)
Patients with any COVID-19-related TEAEs, n (%)	N/A	N/A	14 (3.1)	8 (3.5)
CTCAE Grade ≥3	N/A	N/A	1 (0.2)	5 (2.2)
Serious	N/A	N/A	1 (0.2)	5 (2.2)
Treatment-related	N/A	N/A	0	0

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	**Placebo + BSC N=137**	**Fruquintinib + BSC N=456**	**Placebo + BSC N=230**
Treatment-related CTCAE Grade ≥3	N/A	N/A	0	0
Leading to dose reduction	N/A	N/A	0	0
Leading to dose interruption	N/A	N/A	6 (1.3)	4 (1.7)
Leading to treatment discontinuation	N/A	N/A	0	1 (0.4)
Treatment-related leading to dose reduction	N/A	N/A	0	0
Treatment-related leading to dose interruption	N/A	N/A	0	0
Treatment-related leading to treatment discontinuation	N/A	N/A	0	0
Leading to death	N/A	N/A	0	1 (0.4)

Bold represents changes made vs the table in the CS (Document B)
Source: FRESCO final CSR (2), FRESCO-2 final CSR (3)
[a]Of note, there was 1 patient (of the 49 patients) with a serious TEAE of death due to disease progression (the coded PT by MedDRA, version 25.0) reported in the global safety database but not captured in the EDC at the time of DBL. For this patient, this was the only serious TEAE of CTCAE Grade 5; this TEAE was not treatment related and did not lead to study drug interruption, reduction, or treatment discontinuation. In addition, this patient had an AE in EDC with CTCAE Grade 3 (the coded PT as "proteinuria" by MedDRA, version 25.0). The original statistical outputs were not updated; hence, this note serves to remind the reviewer when reviewing the original outputs relevant to the AE summaries (i.e. Table 14.3.1.1 reflects the number of participants [n=48] with TEAEs leading to death per the original statistical output without the additional participant)
Key: AESI, adverse event of special interest; BSC, best supportive care; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; N/A, not applicable; TEAE, treatment-emergent adverse event.

Replacement Table 22: Comparison of BNF and eMIT costs for concomitant ~~and subsequent~~ medicines

Medicine	Pack size	BNF price per pack	eMIT price per pack
Paracetamol 500mg	100	£2.34	£0.84
Ibuprofen 400mg	84	£2.87	£1.00
Lorazepam 1mg	28	£1.41	£3.36
Macrogol 3350 1mg	**20**	**£3.29**	**£1.99**
Dexamethasone 2mg	50	£3.13	£2.32
Metoclopramide 10mg	28	£0.35	£0.72
Furosemide 40mg	**28**	**£0.57**	**£0.27**
Metoclopramide 10mg	**28**	**£0.35**	**£0.36**
Potassium chloride 20mg	**30**	**£20.19**	**£3.42**

Medicine	Pack size	BNF price per pack	eMIT price per pack
Colecalciferol 400mg	**60**	**£1.70**	**£0.63**
~~Fluorouracil 500mg~~	~~1~~	~~£3~~	~~£3.43~~
~~Oxaliplatin 50mg~~	~~1~~	~~£20~~	~~£6.47~~
~~Capecitabine 150mg~~	~~60~~	~~£9~~	~~£8.10~~
~~Irinotecan 100mg~~	~~1~~	~~£13~~	~~£20.46~~

Bold represents requested changes vs the EAG report and s~~trikethrough~~ represents where deletion required
Key: BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool

Replacement Table 25 Summary features of QALY shortfall analysis

Remaining QALYs	Regorafenib	Trifluridine/tipiracil	BSC
Without disease	12.89	12.89	12.89
With disease	0.57	0.58	0.42
Absolute QALY shortfall	12.32	12.31	12.48
Proportional QALY shortfall	95.57%	95.50%	96.78%
QALY weight	x1.7	x1.7	x1.7

Key: BSC, best supportive care; QALYs, quality adjusted life years.

Replacement Table 26 Base case analyses (fully incremental) conducted by the company [reproduced from Tables 72 and 74 of Document B of the CS and Table 41 of the company's clarification response]

Intervention	Total Costs £	Total Lys	Total QALYs	Incremental Cost	Incremental QALY 1.0	Incremental QALY 1.2	Incremental QALY 1.7	ICER 1.0	ICER 1.2	ICER 1.7
Base case results (fully incremental analysis) – PAS price										
BSC	[redacted]	[redacted]	[redacted]							
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine/tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case results, probabilistic sensitivity analysis (fully incremental)										
BSC	[redacted]	–	[redacted]							
Regorafenib	[redacted]	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Intervention	Total Costs £	Total Lys	Total QALYs	Incremental Cost	Incremental QALY 1.0	Incremental QALY 1.2	Incremental QALY 1.7	ICER 1.0	ICER 1.2	ICER 1.7
Trifluridine/tipiracil	[redacted]	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold represents requested changes vs the EAG report. Note application of CON marking to ICERs)
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Replacement Table 27 Company preferred deterministic and probabilistic base case assumptions (pairwise comparisons) [reproduced from Tables 72 and 74, Document B of the CS and Table 42 of the company's clarification response]

Technologies	Total costs (£)	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALYs x1 weighting	Incremental QALYs x1.7 weighting	Pairwise ICER x1 weighting	Pairwise ICER x1.7 weighting
Deterministic analysis								
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	–	–		–		[redacted]
Probabilistic analysis								
BSC	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	–	-	-	–	-	–

Bold represents requested changes vs the EAG report. Note application of CON marking to ICERs)
Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs quality adjusted life years.

Replacement Table 33 EAG conducted deterministic analyses (pairwise comparisons, QALYs unweighted)

Scenario	ICER versus Regorafenib			ICER versus Trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)
0. Company preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Independently fitted Fruq. and BSC OS /PFS curves	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	ICER versus Regorafenib			ICER versus Trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)	Inc. Cost	Inc. QALY (1.0)	ICER (1.0)
2. Independently fitted OS and PFS curves for Regorafenib and trifluridine-tipiracil	[redacted]								
3. Scenarios 1 & 2 combined	[redacted]								
4. Fruquintinib TTD curve (Generalised gamma)	[redacted]								
5. Regorafenib and trifluridine-tipiracil TTD curves based on median time on treatment	[redacted]								
6. Scenarios 4 & 5 combined	[redacted]								
7. Trial specific RDIs applied to each comparator	[redacted]								
8. Apply eMIT prices for concomitant treatments	[redacted]								
9. Apply additional monitoring costs for regorafenib (2 x medical oncologist visits)	[redacted]								
10. Subsequent treatments based on company sought clinical expert opinion	[redacted]								
11. Duration of subsequent treatments (8 weeks)	[redacted]								
12. Scenarios 10 & 11 combined	[redacted]								
13. EAG preferred base case analysis (Scenarios 3, 6, 7, 8, 9 & 12 combined)	[redacted]								
14. EAG base case with FRESCO clinical data only	[redacted]								
15. EAG base case with FRESCO-2 clinical data only	[redacted]								

Bold represents requested changes vs the EAG report. Note application of CON marking to ICERs)
Key: BSC, best supportive care; eMIT, drugs and pharmaceuticals electronic marketing information tool; LY, life years; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; RDI. Relative dose intensity; TTD, time to treatment discontinuation.

Replacement Table 34: EAG conducted deterministic analyses (pairwise comparisons, QALY severity weighting = 1.7)

Scenario	ICER versus Regorafenib			ICER versus Trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)
0. Company preferred base-case	[redacted]								
1. Independently fitted Fruq and BSC OS / PFS curves	[redacted]								

Scenario	ICER versus Regorafenib			ICER versus Trifluridine-tipiracil			ICER versus BSC		
	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)	Inc. Cost	Inc. QALY (1.7)	ICER (1.7)
2. Independently fitted OS and PFS curves for Regorafenib and trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Scenarios 1 & 2 combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Fruquintinib TTD curve (Generalised gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Regorafenib and trifluridine-tipiracil TTD curves based on median time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Scenarios 4 & 5 combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Trial specific RDIs applied to each comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Apply eMIT prices for concomitant treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Apply additional monitoring costs for regorafenib (2 x medical oncologist visits)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Subsequent treatments based on company sought clinical expert opinion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11. Duration of subsequent treatments (8 weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12. Scenarios 10 & 11 combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13. EAG preferred base case analysis (Scenarios 3, 6, 7, 8, 9 & 12 combined)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14. EAG base case with FRESCO clinical data only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15. EAG base case with FRESCO-2 clinical data only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold represents requested changes vs the EAG report. Note application of CON marking to ICERs).
Key: BSC, best supportive care; eMIT, drugs and pharmaceuticals electronic marketing information tool; LY, life years; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; RDI. Relative dose intensity; TTD, time to treatment discontinuation.