SMC2748

# fruquintinib hard capsule (Fruzaqla®)

## Takeda Pharmaceutical Company Limited

04 April 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE**: following a full submission assessed under the end of life and orphan equivalent medicine process

**fruquintinib (Fruzaqla®)** is not recommended for use within NHSScotland.

**Indication under review**: treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without an anti-VEGF therapy, and if RAS wildtype and medically appropriate, an anti-EGFR therapy.

Fruquintinib, compared with placebo, significantly improved overall survival in adults with mCRC who had been previously treated with available therapies.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

The submitting company has indicated their intention to make a resubmission.

**Chair**
**Scottish Medicines Consortium**

# 1. Clinical Context

### 1.1. Medicine background

Fruquintinib is a tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3 with antitumor effects resulting from suppression of tumour angiogenesis and tumour deprivation of nutrients and oxygen. It is given orally, 5 mg once daily for the first 21 days of 28-day cycles and treatment is continued until disease progression or unacceptable toxicity.[1]

### 1.2. Disease background

Metastases are present at diagnosis for about 15% to 30% of patients with colorectal cancer and they subsequently develop in about 20% to 50% of patients with initially localised disease. They commonly affect the liver, lung, peritoneum and lymph nodes. As mCRC is incurable and life-limiting, treatment aims to improve symptoms, delay progression and extend survival while maintaining quality of life.[2]

### 1.3. Treatment pathway and relevant comparators

First- and second-line treatment of mCRC typically comprises fluoropyrimidine chemotherapy in combination with oxaliplatin or irinotecan (FOLFOX or FOLFIRI), with some patients also receiving targeted therapies.[2,3] The epidermal growth factor receptor (EGFR) inhibitor, cetuximab, is accepted by SMC (advice number 1012/14) for use in combination with FOLFOX or FOLFIRI in the first-line setting and the vascular endothelial growth factor (VEGF) inhibitor, aflibercept, is accepted by SMC (advice number 878/13) for use second-line in combination with FOLFIRI for patients previously treated with FOLFOX. Recently, the third-line treatment, trifluridine-tipiracil, had its licence extended to include use in combination with bevacizumab (a VEGF inhibitor). However, the recency of SMC advice (SMC2654; August 2024) precludes this combination being considered as a comparator in this submission. In practice, fruquintinib may be an alternative to regorafenib or, in patients who are unable to receive bevacizumab, to trifluridine-tipiracil alone. In late stage mCRC, best supportive care (BSC) is an option preferred by some patients. [3]

### 1.4. Category for decision-making process

**Eligibility for interim acceptance decision option**

Fruquintinib has received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway.

**Eligibility for a PACE meeting**

Fruquintinib meets SMC end of life and orphan equivalent criteria for this indication.

# 2. Summary of Clinical Evidence

### 2.1. Evidence for the licensed indication under review

Clinical evidence is from the FRESCO-2 study (in North America, Europe, Asia and Australia), supported by the FRESCO study (in China).[2,4,5] These are detailed in Table 2.1.

**Table 2.1. Overview of relevant studies.[2,4,5]**

| Criteria | FRESCO-2 | FRESCO |
|---|---|---|
| Study design | Double-blind, phase III. | Double-blind, phase III. |
| Eligible patients | Adults (≥18 years or ≥20 years in Japan) with mCRC who had been treated with all standard treatments, including FOLFOX, FOLFIRI, anti-VEGF therapy, anti-EGFR therapy if RAS wild type, and either trifluridine-tipiracil and/or regorafenib. ECOG performance status 0 or 1. | Adults (18 to 75 years) with mCRC who had failed at least two prior lines of standard chemotherapy for metastatic disease. No prior anti-VEGFR therapy. ECOG performance status 0 or 1. |
| Treatments | Fruquintinib 5 mg orally once daily for 21 days of 28-day cycle or placebo. Continued until disease progression or unacceptable toxicity. Plus BSC. | Fruquintinib 5 mg orally once daily for 21 days of 28-day cycle or placebo. Continued until disease progression or unacceptable toxicity. Plus BSC. |
| Randomisation | Randomised in 2:1 ratio to fruquintinib or placebo, stratified by RAS (wild type or mutant); previous therapy (trifluridine-tipiracil or regorafenib or both); and metastatic disease (≤18 or >18 months). | Randomised in 2:1 ratio to fruquintinib or placebo stratified by RAS (wild type or mutant) and prior use of VEGF inhibitor treatment (yes or no). |
| Primary outcome | Overall survival in ITT, defined as time to death from any cause. | Overall survival in ITT, defined as time to death from any cause. |
| Secondary outcome | PFS by investigator on RECISTv1.1 in ITT; time to progression or death. | PFS by investigator on RECISTv1.1 in ITT; time to progression or death. |
| Statistical analysis | PFS included in hierarchical strategy. | No control for multiplicity. |

BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; FOLFIRI = 5-fluroruracil, folinic acid and irinotecan; FOLFOX = 5-fluroruracil, folinic acid and oxaliplatin; ITT = intention-to-treat (that is, all randomised patients); mCRC = metastatic colorectal cancer; PFS = progression-free survival; RECISTv1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

In both studies, fruquintinib, compared with placebo, resulted in statistically significant improvement in the primary outcome, overall survival (OS), and the key secondary outcome, progression-free survival (PFS), as detailed in Table 2.2 below.[2,4,5]

**Table 2.2: Primary and key secondary outcome of FRESCO-2 and FRESCO.[2,4,5,6]**

| | FRESCO-2 | | FRESCO | |
|---|---|---|---|---|
| | **Fruquintinib** | **Placebo** | **Fruquintinib** | **Placebo** |
| | **n=461** | **n=230** | **n=278** | **n=138** |
| **Primary outcome, OS** | | | | |
| Deaths | 317 | 173 | 188 | 109 |
| Hazard ratio (95% CI), p-value | 0.66 (0.55 to 0.80), p<0.001 | | 0.65 (0.51 to 0.83), p<0.001 | |
| Median, months | 7.4 | 4.8 | 9.3 | 6.6 |
| KM estimated OS at 6 months | 60% | 42% | 70% | 54% |
| **Key secondary outcome, PFS assessed by investigator on RECISTv1.1** | | | | |
| Events | 392 | 213 | 235 | 125 |
| Hazard ratio (95% CI), p-value | 0.32 (0.27 to 0.39), p<0.001 | | 0.26 (0.21 to 0.34) | |
| Median, months | 3.7 | 1.8 | 3.7 | 1.8 |
| KM estimated PFS at 3 months | 60% | 18% | 63% | 11% |
| **Best objective response assessed by investigator on RECISTv1.1** | | | | |
| Objective response,* n (%) | 7 (1.5) | 0 | 13 (4.7) | 0 |
| Complete response, n (%) | 0 | 0 | 1 (0.4) | 0 |

CI = confidence interval; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; RECISTv1.1 = Response Evaluation Criteria in Solid Tumours version 1.1. * Objective response = complete or partial response.

### 2.2. Health-related quality of life outcomes

In FRESCO-2, health-related quality of life was assessed using European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and EuroQol 5 dimension 5-level (EQ-5D-5L) questionnaires. In general, there were no substantial differences between the treatment groups.[2]

### 2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

The company provided a network meta-analysis (NMA) to compare fruquintinib versus regorafenib, trifluridine-tipiracil and BSC, as detailed in Table 2.3 below. For the comparisons of fruquintinib versus regorafenib and versus trifluridine-tipiracil the credible intervals (CrI) around the hazard ratio (HR) for OS cross one, suggesting no substantial difference between the groups, and for PFS, they do not cross one in the fixed effect (FE) model but do in the random effects (RE) model.

**Table 2.3: Summary of indirect treatment comparison**

| Criteria | Overview |
|---|---|
| Design | NMA. |
| Population | Patients with mCRC who have been previously treated with or are not considered candidates for available therapies. |
| Comparators | Regorafenib, trifluridine-tipiracil, and BSC. |
| Studies included | Fruquintinib-BSC versus placebo-BSC: FRESCO-2; FRESCO; Xu 2017.[4,5,7]<br>Regorafenib-BSC versus placebo-BSC: CORRECT; CONCUR.[8,9]<br>Trifluridine-tipiracil-BSC versus placebo-BSC: RECOURSE; TERRA; Yoshino 2012.[10-12] |
| Outcomes | OS and PFS. |
| Results | OS (FE model): the HR (95% CrI) for fruquintinib versus regorafenib was 0.93 (0.75 to 1.16); trifluridine-tipiracil was 0.95 (0.78 to 1.15); and BSC was 0.66 (0.57 to 0.76).<br>PFS (FE model): the HR (95% CrI) for fruquintinib versus regorafenib was 0.66 (0.54 to 0.81); trifluridine-tipiracil was 0.67 (0.55 to 0.80); and BSC was 0.30 (0.26 to 0.34).<br>PFS (RE model): the HR (95% CrI) for fruquintinib versus regorafenib was 0.69 (0.46 to 1.13); trifluridine-tipiracil was 0.68 (0.46 to 1.04); and BSC was 0.29 (0.22 to 0.39). |

BSC = best supportive care; CrI = credible interval; FE = fixed effect; HR = hazard ratio; mCRC = metastatic colorectal cancer; NMA = network meta-analysis OS = overall survival; PFS = progression-free survival; RE = random effects.

## 3. Summary of Safety Evidence

The regulator noted that the safety profile of fruquintinib is generally in accordance with what is expected for a medicinal product involving the VEGF inhibition pathway and with what has been previously reported for heavily pretreated mCRC patients. Adverse events typical of VEGF inhibition include hypertension, dermatological toxicity, thyroid dysfunction, proteinuria, haemorrhages, gastrointestinal perforation, infections, embolic and thrombotic events and hepatic function abnormal. These are included in the summary of product characteristics.[2]

In the FRESCO-2 study, within the fruquintinib and placebo groups, 99% (451/456) and 93% (213/230) of patients had an adverse event and these were considered treatment-related in 87% and 56%, respectively. Serious adverse events were reported by 38% of patients in both groups and were considered treatment-related in 9.4% and 3.5% of patients in the fruquintinib and placebo groups, respectively. Adverse events led to dose reduction in 24% versus 3.9%; dose interruption in 47% versus 27%; and treatment discontinuation in 20% and 21%, respectively.[2]

In the FRESCO-2 study, within the fruquintinib and placebo groups, common adverse events included hypertension (37% and 8.7%), hypothyroidism (21% and 0.4%), asthenia (34% and 23%), palmar-plantar erythrodysaesthesia syndrome (19% and 2.6%), diarrhoea (24% and 10%), constipation (17% and 9.6%), nausea (17% and 18%), vomiting (14% and 12%), abdominal pain (18% and 16%), decreased appetite (27% and 17%), decreased weight (12% and 9.1%), stomatitis (15% and 3.5%), proteinuria (17% and 5.2%), fatigue (20% and 16%), dysphonia (16% and 5.2%), arthralgia (11% and 4.3%), back pain (10% and 7.4%), aspartate aminotransferase (AST) increased (11% and 4.3%) and alanine aminotransferase (ALT) increased (10% and 3.9%).[2]

The safety profile in FRESCO appears similar to that in FRESCO-2.[2]

# 4. Summary of Clinical Effectiveness Considerations

### 4.1. Key strengths

- In FRESCO-2, fruquintinib, compared with placebo, resulted in statistically significant improvement in median OS by 2.6 months. Although modest, the regulator considered this clinically meaningful, as it concerns a very late-line setting. The 1.9 months improvement in median PFS, although short, was also considered clinically meaningful when evaluated together with OS.[2]
- Results of FRESCO-2 are supported by FRESCO, where fruquintinib, compared with placebo, also resulted in statistically significant improvement in median OS by 2.7 months and PFS by 1.9 months.[2,5]

### 4.2. Key uncertainties

- Fruquintinib's marketing authorisation allows it to be used in the third-line or later setting. The population in FRESCO-2 was at a later stage of treatment, with 96% of the study population receiving fruquintinib in the fourth-line or later setting and with 73% receiving treatment at fifth-line or later. In FRESCO, patients had fruquintinib at an earlier stage, with 69% of patients receiving it at fourth-line or earlier. The magnitude of benefit with fruquintinib appears comparable across the studies.[2,4,5]
- The population in FRESCO-2 differs from the licensed indication, which requires patients to have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without an anti-VEGF therapy, and if RAS wildtype and medically appropriate, an anti-EGFR therapy. In addition to this, the FRESCO-2 population had also been previously treated with regorafenib and/or trifluridine-tipiracil.[1,2]
- The comparator in both FRESCO-2 and FRESCO was placebo plus BSC. This may not reflect practice where active treatment, such as regorafenib or trifluridine-tipiracil (with or without bevacizumab) may be administered. To address the lack of comparative evidence versus relevant comparators, an indirect NMA comparison of fruquintinib versus regorafenib and versus trifluridine-tipiracil was presented.
- From the NMA results, the company has concluded that fruquintinib has an advantage over regorafenib and trifluridine-tipiracil for OS and PFS. However, the CrI around the HR for OS cross one, suggesting no substantial difference. In the FE model (but not the RE model), CrI

around the HR for PFS suggest a possible advantage for fruquintinib. However, there is uncertainty around this due to limitations of the indirect comparison.

- The NMA is limited by statistical heterogeneity across the regorafenib studies. Also, there were differences across all studies in prior treatments; in the three phase III international studies (FRESCO-2, CORRECT and RECOURSE) all or almost all (96% to 97%) patients had previously had anti-VEGF therapy. Whereas rates in the Asian studies were 19% to 32%, except in the phase II Yoshino 2012 study (78% to 82%). Some subgroup analyses indicated greater magnitude of benefit with fruquintinib, regorafenib and trifluridine-tipiracil in those without prior exposure to anti-VEGF therapy. Although prior anti-VEGF therapy may be a treatment-effect modifier, no adjustment has been made for this. Statistical advice highlighted that there was limited justification for choosing FE models and that RE models may have been more appropriate due to heterogeneity. For the PFS analyses, the statistical significance, and therefore interpretation, of the results differs between the FE and RE models. Due to these limitations, the company's conclusions are uncertain.
- Fruquintinib has been granted an Innovation Passport as part of the Innovative Licensing and Access Pathway. However, no efficacy data are awaited in this indication from ongoing studies.

### 4.3. Clinical expert input

Clinical experts consulted by SMC considered that fruquintinib could fulfil an unmet need for additional effective treatments in this setting and is a therapeutic advancement due to its clinical efficacy and tolerability. They consider that it would be used in place of alternative treatment options, such as regorafenib.

## 5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of fruquintinib, as an orphan-equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

- Patients at third-line or later treatment of mCRC have a short life expectancy and poor quality of life due to symptoms of the disease and adverse events from previous chemotherapies. They may not be able to participate in work, education and caring responsibilities or enjoying sports and socialising with their family and friends, which may be particularly distressing for families with young children. Their available treatment options are limited. Altogether, their condition has a huge negative psychological impact, with many patients suffering anxiety and depression. There is an unmet need for additional effective therapies with acceptable tolerability.
- In heavily pre-treated patients with mCRC, fruquintinib plus BSC, compared with BSC alone, increased overall survival on average by about two and a half months and PFS by about two months. This was achieved with a manageable safety profile and convenient once daily oral dosing. Fruquintinib provides an additional treatment option with a targeted action

that may reduce side-effects allowing patients to maintain treatment and its benefits for longer.

- Improved overall survival and PFS would give the patient additional time when their symptoms are controlled and they can lead a more normal life, including returning to sports, which bring physical and psychological benefits. The value of additional time with family and friends cannot be overstated, especially for families with young children. Also, it may provide a period when there is a reduction in the caring responsibilities of the patient's family. Many patients are aware of fruquintinib and its potential benefits. Accessing this novel medicine may provide reassurance and reduce their anxiety. Overall, fruquintinib could improve the mental health of the patient and their family.
- Clinical experts noted that fruquintinib is likely to be given after the standard third-line therapy: trifluridine-tipiracil plus bevacizumab. In this context, it is expected to replace and reduce the use of regorafenib. They noted that there is clinical experience in the service of using similar multi-kinase inhibitors that have manageable safety profiles. Patients advised that they are happy to risk any potential adverse events associated with fruquintinib to gain the benefits of improved overall and PFS.

**Additional Patient and Carer Involvement**

We received a patient group submission from Bowel Cancer UK, which is a registered charity. Bowel Cancer UK has received 3.5-4% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from the patient group participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

## 6. Summary of Comparative Health Economic Evidence

### 6.1. Economic case

An economic case was presented and is summarised in Table 6.1.

**Table 6.1 Description of economic analysis**

| Criteria | Overview |
|---|---|
| Analysis type | Cost-utility analysis. |
| Time horizon | 10 years. |
| Population | Adult patients with mCRC who have been previously treated with available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without an anti-VEGF therapy and, if RAS wildtype and medically appropriate, an anti-EGFR therapy. |
| Comparators | Three comparators were included. These were regorafenib, trifluridine-tipiracil, and best supportive care (BSC). BSC was defined within the FRESCO and FRESCO-2 study protocol as any treatment necessary for health and not anticipated to interfere with study drug and was determined locally by the investigator. BSC costs were included in all active treatment arms. |
| Model description | A three-state partitioned survival model was used, comprising of three mutually exclusive health states: progression-free, post-progression, and death. Patients start in the progression-free health state, and in each cycle may either remain progression-free, transition to post-progression, or transition directly to death. In each cycle, patients in the post-progression state may subsequently transition to death. |
| Clinical data | The key source of clinical evidence for fruquintinib and BSC was pooled data from the FRESCO and FRESCO-2 studies.[2,4,5] These data were used to inform modelled patient baseline |

| | |
|---|---|
| | characteristics, OS, PFS, time to treatment discontinuation (TTD), adverse events, relative dose intensity (RDI), and subsequent therapies. The key source of clinical evidence for trifluridine-tipiracil and regorafenib was the NMA. The hazard ratios from the NMA were used to inform modelled OS, PFS and TTD (through a PFS proxy). Adverse events were from the key studies aligned with the efficacy data. |
| Extrapolation | Fruquintinib and BSC OS were extrapolated using a joint generalised gamma distribution. Trifluridine-tipiracil and regorafenib OS were estimated by applying their respective OS hazard ratios versus fruquintinib of 1.05 (95% credible interval (CrI) 0.87 to 1.28) and 1.08 (95% CrI 0.86 to 1.33) to the fruquintinib OS extrapolation. A fixed effects model was selected for the base case extrapolations.<br><br>Fruquintinib and BSC PFS were extrapolated using a joint log-normal distribution. Trifluridine-tipiracil and regorafenib PFS were estimated by applying their respective PFS hazard ratios versus fruquintinib of 1.49 (95% CrI 1.25 to 1.82) and 1.52 (95% CrI 1.23 to 1.85) to the fruquintinib PFS extrapolation.<br><br>Fruquintinib TTD was extrapolated using a log-normal distribution. No TTD was applied in the BSC arm. Trifluridine-tipiracil and regorafenib TTD were estimated through a PFS proxy, by applying their respective PFS hazard ratios versus fruquintinib to the fruquintinib TTD extrapolation. |
| Quality of life | Health state utility values were derived from EQ-5D-5L data in FRESCO-2 mapped to EQ-5D-3L,[13] with progression-free and progressed disease utility values of 0.71 and 0.65, respectively. Adverse event utility decrements were included. Utility values were also adjusted for age and gender. |
| Costs and resource use | Medicine acquisition, concomitant medication (representing BSC), subsequent treatment, adverse event, health state and end of life costs were included. The cost of subsequent treatments was applied as a one-off cost upon progression and assumed 4 weeks of treatment. An RDI of 89.6% was applied to fruquintinib, with the same RDI assumed for regorafenib, and trifluridine-tipiracil. |
| PAS | A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.<br><br>A PAS discount is in place for regorafenib, and trifluridine-tipiracil and these were included in the results used for decision-making by using estimates of the comparator PAS price. |

### 6.2. Results

SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

### 6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 6.3. Sensitivity analysis noted in scenarios C1, C2 and C3 represent combined scenarios using various aspects set out in Table 6.3.

**Table 6.3: Scenario analyses**

| | Parameter | Base case | Scenario |
|---|---|---|---|
| | ***Base case*** | - | - |
| 1 | Time horizon | 10 years | 5 years |
| 2a | PFS extrapolation (BSC and fruquintinib) | Joint curves: log-normal | Joint curves: gen. gamma |
| 2b | | | Individual fits: log -normal |

| | | | |
|---|---|---|---|
| 2c | | | Individual fits: log -logistic |
| 3a | OS extrapolation (BSC and fruquintinib) | Joint curves: gen. gamma | Joint curves: log-normal |
| 3b | | | Individual fits: log -normal |
| 3c | | | Individual fits: gen - gamma |
| 4a | OS hazard ratio regorafenib vs fruquintinib | 1.08 | 0.86 |
| 4b | | | 1 |
| 4c | | | 1.33 |
| 5a | OS hazard ratio trifluridine-tipiracil vs fruquintinib | 1.05 | 0.87 |
| 5b | | | 1 |
| 5c | | | 1.28 |
| 6a | PFS hazard ratio regorafenib vs fruquintinib | 1.52 | 1.23 |
| 6b | | | 1.85 |
| 7a | PFS hazard ratio trifluridine-tipiracil vs fruquintinib | 1.49 | 1.25 |
| 7b | | | 1.82 |
| 8a | NMA approach | Fixed-effects model | Random-effects model |
| 8b | | | Random-effects model PFS HR = OS HR = 1 |
| 9 | TTD extrapolation fruquintinib | Log-normal | Gen. gamma |
| 10a | TTD | Fruquintinib extrapolation and PFS HR for regorafenib and trifluridine-tipiracil | Treat to progression |
| 10b | | | Regorafenib and trifluridine-tipiracil "median treatment duration" |
| 11 | Grade 1–2 AEs | Included | Excluded |
| 12a | Subsequent treatments | Pooled trial data | Clinical opinion |
| 12b | | | SMC clinical opinion |
| 13 | Subsequent treatments | 4 weeks | 1 week |
| 14 | Disutilities from AEs | Include | Exclude |
| 15a | RDI | Equal to fruquintinib (89.6%) | 100% all treatments |
| 15b | | | Key clinical trials |
| 16 | Progressed disease utility decrement | Regression model FRESCO-2 (0.06) | SMC1221/17 (0.14) |
| C1 | 1, 10b, 12b, 15b (Time horizon 5 years, median TTD, SMC clinical opinion subsequent treatment, RDI key clinical trials) | | |
| C2 | 1, 10b, 12b, 15b, 2c, 3c, 8a (Time horizon 5 years, median TTD, SMC clinical opinion subsequent treatment, RDI key clinical trials, conservative individual fit PFS and OS extrapolations, random effects model) | | |
| C3 | 1, 10b, 12b, 15b, 2c, 3c, 8b (Time horizon 5 years, median TTD, SMC clinical opinion for subsequent treatment, RDI key clinical trials, conservative individual fit PFS and OS extrapolations, random effects model PFS=OS=1) | | |

Abbreviations: AE = adverse events; BSC = best supportive care; C= combined scenario; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; RDI = relative dose intensity.

### 6.4. Key strengths

- The model structure was appropriate to capture disease progression for patients receiving treatment for mCRC.
- The company's systematic literature review facilitated a comparison of utility values used in other relevant mCRC economic evaluations considered by SMC.
- Pooled fruquintinib TTD Kaplan-Meier (KM) data were mature with 94% of patients having discontinued at the end of follow-up.
- The pooled OS and PFS data for fruquintinib and BSC indicated maturity, 68% and 77% of patients experienced an OS event, respectively, at the end of follow-up (23.3 months). 85% and 92% of patients experienced a PFS event, respectively, at maximum follow-up (22.1 months).

### 6.5. Key uncertainties

- There were uncertainties in the extrapolation of PFS and OS outcomes. Firstly, in the base case fruquintinib and BSC PFS and OS were each extrapolated using jointly fitted distributions. However, there was an indication that the proportional hazards assumption required for this approach was violated. As a result, independent extrapolations were explored (Scenarios 2b, 2c, 3b, 3c). Secondly, there were several limitations of the NMA, which increased uncertainty in the relative PFS and OS benefits of fruquintinib versus regorafenib and trifluridine-tipiracil. The HRs applied to estimate regorafenib and trifluridine-tipiracil PFS and OS outcomes showed wide confidence intervals and crossed one for OS (Scenarios 4 to 7). In addition, SMC statistical advice noted that the RE model may have been more appropriate given the reported heterogeneity between the studies, which reduced the relative efficacy of fruquintinib versus regorafenib and trifluridine-tipiracil (Scenario 8a). The random-effects model also did not demonstrate a statistically significant improvement in PFS or OS benefits of fruquintinib versus regorafenib and trifluridine-tipiracil (Scenario 8b).
- There was uncertainty in the TTD extrapolations of regorafenib and trifluridine-tipiracil. As PFS HRs were applied to fruquintinib TTD to estimate the TTD extrapolations for these comparators, this assumed treatment discontinuation was proportional between treatments and constant over time, which may not hold given different adverse event profiles. Alternatives were considered in scenario analysis. The first set TTD equal to PFS (Scenario 10a). The second used a "median treatment duration" approach to calibrate an exponential curve through the reported median treatment duration for regorafenib (CORRECT, 1.7 months) and trifluridine-tipiracil (RECOURSE and Yoshino 2012 pooled data, 1.5 months), which generated a median modelled TTD aligned with these studies (Scenario 10b). The submitting company highlighted several limitations with the method and viewed this as underpredicting median TTD for these treatments when compared to real world evidence, indicating the scenario as a conservative one. However, the estimated median TTD of the scenario showed alignment with median TTD from the clinical studies (CORRECT for regorafenib and RECOURSE for trifluridine-tipiracil) and company clinical expert opinion for trifluridine-tipiracil.

- The RDI applied to the comparator treatments of regorafenib and trifluridine-tipiracil was assumed to be equal to fruquintinib. However, this may increase uncertainty in the base case results given the different adverse event profiles. A scenario analysis was therefore considered that applied respective RDI proportions from the CORRECT and RECOURSE studies for regorafenib (78.9%) and trifluridine-tipiracil (89.0%) (Scenario 15b).
- There was uncertainty in the subsequent treatments applied in the base case. These were drawn from the FRESCO and FRESCO-2 studies, but some of these are not recommended by SMC for use in mCRC. As a result, a scenario was provided where subsequent anti-cancer treatments were based on Scottish company clinical expert opinion (Scenario 12a). SMC clinical experts viewed these treatments as reasonable but highlighted that the number of patients receiving fourth-line regorafenib, after third-line trifluridine-tipiracil, could be less than 50% (at most 20%) (Scenario 12b). However, this remains an uncertain area given the evolving treatment pathway.
- The utility decrement from progression free to progressed disease was smaller than in previous SMC assessments in mCRC. However, a scenario was considered that applied a larger decrement from SMC1221/17 (Scenario 16).
- The submitting company included grade 1-2 adverse events in the economic evaluation, with an assumed 0.01 utility decrement. It is not common to include grade 1-2 adverse events in economic cases. However, a scenario was considered to exclude these from the analysis (Scenario 11).

## 7. Conclusion

The Committee considered the benefits of fruquintinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as fruquintinib is an orphan-equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept fruquintinib for use in NHSScotland.

## 8. Guidelines and Protocols

Metastatic colorectal cancer: European Society for Medical Oncology (ESMO) Clinical Practice Guideline for diagnosis, treatment and follow-up was published in 2023.[3]

Scottish Intercollegiate Guidelines Network (SIGN). SIGN 126: Diagnosis and management of colorectal cancer was published in 2011 and revised in 2016.[14]

## 9. Additional Information

### 9.1. Product availability date

20 September 2024

**Table 9.1 List price of medicine under review**

| Medicine | Dose regimen | Cost per cycle (£) |
|---|---|---|
| **Fruquintinib** | **5 mg orally each day for first 21 days in 28-day cycle** | **3,950** |

*Costs from Dictionary of Medicines and Devices Browser accessed on 28 January 2025. Costs do not take any patient access schemes into consideration.*

## 10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 462 patients eligible for treatment with fruquintinib in year 1 and 472 patients in year 5. SMC is unable to publish the budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

**References**

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13. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. Pharmacoeconomics 2023; 41(2):199-207.

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This assessment is based on data submitted by the applicant company up to and including 14 February 2025.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context**:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.