Fruquintinib (colorectal cancer)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma – isoform B
BSC	best supportive care
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
dMMR	mismatch repair deficient
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
InGef	Institut für angewandte Gesundheitsforschung Berlin (Institute for Applied Health Research Berlin)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	microsatellite instability-high
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
Q-TWiST	quality-adjusted time without symptoms or toxicity
RAS	rat sarcoma viral oncogene homologue
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SPC	Summary of Product Characteristics
VAS	visual analogue scale
VEGF	vascular endothelial growth factor

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug fruquintinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 10 July 2024.

Research question

The aim of the present report is to assess the added benefit of fruquintinib as monotherapy compared with best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with metastatic colorectal cancer who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents, and anti-epidermal growth factor receptor (EGFR) agents, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of fruquintinib

Therapeutic indication	**ACT[a]**
Monotherapy for the treatment of adults with metastatic colorectal cancer ▪ who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and ▪ who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib[b, c]	BSC[d]

a. Presented is the ACT specified by the G-BA.
b. Withdrawn from the German market.
c. The G-BA describes that, according to the inclusion criteria of the pivotal study for approval, patients must have already been pretreated with available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF therapies, and anti-EGFR therapies (for RAS wild type), as well as trifluridine/tipiracil and/or regorafenib. Furthermore, according to the G-BA it is assumed that patients with BRAF V600E mutation were treated with a BRAF inhibitor, and patients with high-frequency microsatellite instability (MSI-H) or with a mismatch repair deficiency (dMMR) were treated with a checkpoint inhibitor. According to the G-BA, it is assumed that the patients have received all the therapies mentioned or are not eligible for them.
d. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; dMMR: mismatch repair deficiency; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor

The company designated BSC as the ACT, thus following the G-BA's specification.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit.

Study pool and study design

The FRESCO-2 study is used for the benefit assessment. The FRESCO-2 study is a multinational, double-blind RCT comparing fruquintinib + BSC versus placebo + BSC. Patients were included if they were at least 18 years old (in Japan at least 20 years old) and had histologically or cytologically documented metastatic colorectal adenocarcinoma. At study start, patients had to be in good general condition according to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and have an expected survival time of > 12 weeks.

According to the inclusion criteria, patients must have been previously treated with all standard therapies for the metastatic stage of the disease and must have progressed on or been intolerant to treatment with either trifluridine/tipiracil or regorafenib. Standard treatment regimens had to include the following drugs: fluoropyrimidine, oxaliplatin and irinotecan, and an anti-VEGF biological therapy (e.g. bevacizumab, aflibercept, ramucirumab), and, if rat RAS wild type, an anti-EGFR therapy (e.g. cetuximab or panitumumab). In addition, patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours had to be pretreated with immune checkpoint inhibitors, and patients with rapidly accelerated fibrosarcoma – isoform B (BRAF) mutation had to be pretreated with a BRAF inhibitor unless these were unsuitable for the patients.

A total of 691 patients were included and randomly assigned in a ratio of 2:1, either to treatment with fruquintinib + BSC (461 patients) or to treatment with placebo + BSC (230 patients). Stratification factors were RAS mutation status (wild type versus mutant), the time since diagnosis of first metastasis (≤ 18 months versus > 18 months), and prior therapy with trifluridine/tipiracil versus regorafenib versus both trifluridine/tipiracil and regorafenib.

Treatment with fruquintinib was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). Patients in the intervention arm received 5 mg of fruquintinib once daily for 21 consecutive days of the 28-day treatment cycles. Patients in the comparator arm received matching placebo capsules according to the same administration schedule. All patients additionally received concomitant treatment, which could include, but was not limited to, haematological supportive therapies, anti-emetics, and palliative radiation for symptom control. However, any other antineoplastic therapies, including chemotherapy, were not permitted as concomitant treatment. Study treatment was administered until disease progression or occurrence of unacceptable toxicity. Treatment switching from the comparator to the intervention arm was not planned according to the planning of the study.

About 30% of the patients received subsequent therapy after completion of the randomized study treatment.

The primary outcome was overall survival. Patient-relevant outcomes of morbidity, health-related quality of life and side effects were additionally recorded.

The FRESCO-2 study has several uncertainties that are relevant for the present benefit assessment. In particular, this concerns a high number of major protocol violations that occurred during the conduct of the study, the necessary prior therapies in the population of the present research question and the implementation of the ACT. These uncertainties are explained below.

Limitations of the FRESCO-2 study

Study conduct (protocol violations)

Study documents show that 613 (89%) of the patients included in the study had at least one major protocol deviation in the course of the study. The most frequent major protocol deviations during the course of the study concerned missed study procedures (53% of patients in the intervention arm versus 44% in the comparator arm), the dosage of the study medication (51% versus 40%), and the inclusion and exclusion criteria (36% versus 35%).

In the dossier's Module 4 D, the company presented no information on protocol deviations. Based on the available information in Module 5 of the dossier, it remains unclear to what extent the planning of the study was deviated from in detail and how the deviations affected the treatment in the study or the recording of patient-relevant outcomes. Furthermore, the study documents do not contain any information on how a major protocol violation was defined. The available data show differences in the proportion of patients between the study arms, particularly with regard to the major protocol deviations concerning the dosage of the study medication and the missed study procedures. Since it remains unclear overall whether the major protocol deviations have an effect on the available analyses of the FRESCO-2 study, this uncertainty is taken into account when assessing the risk of bias of the results.

Suitability of the study population for the present benefit assessment

In the present therapeutic indication, patients must have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. Patients must also have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib. However, according to the G-BA, regorafenib is no longer on the market in Germany at the time of this benefit assessment. In contrast to pretreatment with trifluridine/tipiracil, pretreatment with regorafenib therefore does not correspond to the German health care context. In the FRESCO-2 study, a large proportion (48%) of patients had also been pretreated with

regorafenib, including 8% of patients pretreated exclusively with regorafenib and not with trifluridine/tipiracil. Nevertheless, the majority of patients had been pretreated with trifluridine/tipiracil. Although the proportion of patients who did not receive trifluridine/tipiracil is low, it remains unclear whether these patients could still have benefited from treatment with trifluridine/tipiracil.

With regard to the other prior therapies specified according to the therapeutic indication, it can be inferred from the available information on protocol violations that patients were also included in the study without fulfilling the inclusion criterion of pretreatment with anti-VEGF therapies before the start of the study. However, at around 96%, the majority of the study population received a corresponding pretreatment. The other required prior therapies according to the present research question were also administered to the majority of patients, in the case of EGFR, immune checkpoint and BRAF inhibitors in relation to the respective population for which these therapies are indicated (RAS wild type, MSI-H and/or dMMR, BRAF mutation).

Overall, it remains unclear whether the results of the FRESCO-2 study are fully transferable to patients in the German health care context due to the limitations in prior therapy described above. This uncertainty is taken into account in the assessment of the certainty of results.

Implementation of the appropriate comparator therapy and administration of subsequent therapies

As described above, patients in the FRESCO-2 study received supportive concomitant treatment, which could include, but was not limited to, haematological supportive therapies, anti-emetics, and palliative radiation for symptom control. However, any other antineoplastic therapies, including chemotherapy, were not permitted as concomitant treatment. This contradicts the guideline on palliative care, which emphasizes that the management and the alleviation of distressing symptoms are a key part of palliative care when treating patients with incurable cancer. Symptom-oriented measures can be implemented on their own or parallel to tumour-related or causal therapies. According to the guideline, an either-or is not appropriate, which is why tumour-specific measures (e.g. radiotherapy, surgical procedures, antitumour drug treatments) should be weighed up against the primary or sole therapeutic goal of symptom relief. The exclusion of further antineoplastic therapies including chemotherapy in the study therefore potentially means a restriction of palliative therapy. Data on subsequent therapies also show that around 1 third of patients who discontinued treatment received at least one further subsequent antineoplastic therapy, including chemotherapy. This high proportion shows that there was a need for further treatment also with systemic therapies after the end of the randomized study medication. It remains unclear whether the administration of additional treatment options in the comparator arm of the study might have been indicated already during the randomized study treatment. Against this

background, there is overall uncertainty as to whether BSC was fully implemented in the FRESCO-2 study or whether there was potentially undertreatment in some of the patients. This uncertainty is taken into account in the assessment of the certainty of results.

Risk of bias and assessment of the certainty of conclusions

The risk of bias across outcomes for the FRESCO-2 study is rated as high due to the great number of major protocol violations in the study, for which it remains unclear to what extent the planning of the study was deviated from and how the deviations affected treatment in the study or the recording of patient-relevant outcomes and thus the available analyses of the FRESCO-2 study. In addition to the high number of major protocol violations in the study, it also remains unclear whether the results of the FRESCO-2 study can be transferred without restriction to the target population in the German health care context. This is due to the fact that patients were included in the study who do not correspond to the population of the present research question with regard to prior therapy. Furthermore, it remains unclear whether BSC was fully implemented in the FRESCO-2 study. Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the FRESCO-2 study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

In addition, there are differences in the duration of treatment and observation between the study arms. This results in uncertainty due to incomplete observations for potentially informative reasons, which also contribute to the high risk of bias of the results for the outcomes in the side effects category (except discontinuation due to AEs).

No suitable data are available for other outcomes in the categories of morbidity and health-related quality of life because the proportions of missing values were too high. Hence, the risk of bias of the results is not assessed for these outcomes.

Results

Mortality

Overall survival

A statistically significant difference in favour of fruquintinib + BSC in comparison with placebo + BSC was shown for the outcome of overall survival. There is a hint of an added benefit of fruquintinib in comparison with BSC.

Morbidity

Health status (EQ-5D VAS) and symptoms (EORTC QLQ-C30)

No suitable data are available for the outcomes of health status (recorded using the EQ-5D visual analogue scale [VAS]) and symptoms (recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]).

There is no hint of an added benefit of fruquintinib in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life (recorded with the EORTC QLQ-C30)

No suitable data are available for the outcome of health-related quality of life (recorded with the EORTC QLQ-C30). There is no hint of an added benefit of fruquintinib in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, discontinuation due to AEs

No statistically significant difference between treatment groups was shown for the outcomes of serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), and discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from fruquintinib in comparison with BSC; greater or lesser harm is therefore not proven.

Specific AEs

Gastrointestinal perforation (SMQ, AEs) and haemorrhages (SMQ, AEs, severe AEs)

No statistically significant difference between treatment groups was shown for the outcomes of gastrointestinal perforation (Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ], AEs) and haemorrhages (SMQ, AEs, severe AEs). In each case, there is no hint of greater or lesser harm from fruquintinib in comparison with BSC; greater or lesser harm is therefore not proven.

Diarrhoea (PT, AEs), hand-foot syndrome (PT, severe AEs), hypertension (SMQ, severe AEs), mucosal inflammation (PT, AEs), stomatitis (PT, AEs), and dysphonia (PT, AEs)

A statistically significant difference between treatment groups to the disadvantage of fruquintinib + BSC compared with placebo + BSC was shown for each of the outcomes of diarrhoea (Preferred Term [PT], AEs), hand-foot syndrome (PT, severe AEs), hypertension (SMQ, severe AEs), mucosal inflammation (PT, AEs), stomatitis (PT, AEs), and dysphonia (PT, AEs). In each case, there is a hint of greater harm from fruquintinib in comparison with BSC.

Abnormal hepatic function (SMQ, SAEs)

A statistically significant difference between treatment groups in favour of fruquintinib + BSC in comparison with placebo + BSC was shown for the outcome of abnormal hepatic function (SMQ, SAEs). There is a hint of lesser harm from fruquintinib in comparison with BSC.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug fruquintinib in comparison with the ACT is assessed as follows:

Overall, there is a hint of major added benefit for the outcome of overall survival. On the other hand, there are several negative effects for outcomes in the side effects category (in different severity categories), ranging from considerable to major extent. At the same time, no suitable data are available on the patient-reported outcomes of symptoms, health status and health-related quality of life. The negative effects and the missing data on the patient-reported outcomes do not completely challenge the positive effect for the outcome of overall survival, but influence the extent of the added benefit in the overall consideration.

In summary, there is a hint of considerable added benefit of fruquintinib in comparison with the ACT BSC for patients with metastatic colorectal cancer who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib.

Table 3 shows a summary of probability and extent of the added benefit of fruquintinib.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Fruquintinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Monotherapy for the treatment of adults with metastatic colorectal cancer ▪ who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and ▪ who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib[b, c]	BSC[d]	Hint of considerable added benefit[e]

a. Presented is the ACT specified by the G-BA.
b. Withdrawn from the German market.
c. The G-BA describes that, according to the inclusion criteria of the pivotal study for approval, patients must have already been pretreated with available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF therapies, and anti-EGFR therapies (for RAS wild type), as well as trifluridine/tipiracil and/or regorafenib. Furthermore, according to the G-BA it is assumed that patients with BRAF V600E mutation were treated with a BRAF inhibitor, and patients with high-frequency microsatellite instability (MSI-H) or with a mismatch repair deficiency (dMMR) were treated with a checkpoint inhibitor. According to the G-BA, it is assumed that the patients have received all the therapies mentioned or are not eligible for them.
d. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
e. The FRESCO-2 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; dMMR: mismatch repair deficiency; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of fruquintinib as monotherapy compared with BSC as ACT in adult patients with metastatic colorectal cancer who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of fruquintinib

Therapeutic indication	**ACT[a]**
Monotherapy for the treatment of adults with metastatic colorectal cancer ▪ who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and ▪ who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib[b, c]	BSC[d]

a. Presented is the ACT specified by the G-BA.
b. Withdrawn from the German market.
c. The G-BA describes that, according to the inclusion criteria of the pivotal study for approval, patients must have already been pretreated with available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF therapies, and anti-EGFR therapies (for RAS wild type), as well as trifluridine/tipiracil and/or regorafenib. Furthermore, according to the G-BA it is assumed that patients with BRAF V600E mutation were treated with a BRAF inhibitor, and patients with high-frequency microsatellite instability (MSI-H) or with a mismatch repair deficiency (dMMR) were treated with a checkpoint inhibitor. According to the G-BA, it is assumed that the patients have received all the therapies mentioned or are not eligible for them.
d. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; dMMR: mismatch repair deficiency; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor

The company designated BSC as the ACT, thus following the G-BA's specification.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on fruquintinib (status: 30 May 2024)
- bibliographical literature search on fruquintinib (last search on 16 May 2024)
- search in trial registries/trial results databases for studies on fruquintinib (last search on 16 May 2024)
- search on the G-BA website for fruquintinib (last search on 21 May 2024)

To check the completeness of the study pool:

- search in trial registries for studies on fruquintinib (last search on 18 July 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: fruquintinib vs. BSC

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
2019-013-GLOB1 (FRESCO-2[c])	Yes	No[d]	Yes[d]	Yes [3]	Yes [4,5]	Yes [6,7]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
d. The sponsor of the study was Hutchison MediPharma Limited. The company (Takeda GmbH) is the exclusive worldwide (outside China) licence holder of fruquintinib.

BSC: best supportive care; CSR: clinical study report; RCT: randomized controlled trial

The FRESCO-2 study is used for the benefit assessment. The study pool is consistent with the study pool of the company. The study is described in the following section.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
FRESCO-2	RCT, double-blind, parallel	Adult patients with metastatic colorectal cancer and ▪ ECOG PS ≤ 1 ▪ Pretreated: ▫ with the following standard therapies: fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies ▫ anti-VEGF therapy ▫ for RAS wild type: anti-EGFR therapy ▫ for MSI-H or dMMR tumours: checkpoint inhibitors[b] ▫ for BRAF-mutant tumours: BRAF inhibitor[b] ▫ progression on or intolerance to trifluridine/tipiracil or regorafenib[c]	Fruquintinib + BSC (N = 461) Placebo + BSC (N = 230)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity Observation[d]: outcome-specific, at most until death, lost to follow-up, withdrawal of consent, or end of study	124 centres in Australia, Austria, Belgium, Czech Republic, Estonia, France, Germany, Hungary, Italy, Japan, Poland, Spain, United Kingdom, United States 8/2020–6/2022[e] Data cut-offs: ▪ 24 September 2021 (interim analysis for futility[f]) ▪ 24 June 2022 (final analysis[g])	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Except patients who are not eligible for these therapies.
c. Patients were considered intolerant if they have received at least one dose of either drug and were discontinued from therapy for reasons other than disease progression. Prior treatment with both therapies (both trifluridine/tipiracil and regorafenib) was permitted.
d. Outcome-specific information is provided in Table 8.
e. According to Module 4 A in the company's dossier, the study was terminated because the planned number of 480 events in the outcome of overall survival for the final analysis had been exceeded.
f. Prespecified after 160 events in the overall survival outcome.
g. According to the study protocol, planned after at least 480 events in the overall survival outcome, performed after 490 events in the overall survival outcome.

AE: adverse event; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; dMMR: mismatch repair deficiency; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; MSI-H: high-frequency microsatellite instability; N: number of randomized patients; RAS: rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

Table 7: Characteristics of the intervention – fruquintinib + BSC vs. placebo + BSC (multipage table)

Study	Intervention	Comparison
FRESCO-2	Fruquintinib 5 mg, orally, once daily on Days 1–21 of each 28-day cycle + BSC[a]	Placebo, orally, once daily on Days 1–21 of each 28-day cycle + BSC[a]
	Dose adjustment[b]: ▪ Fruquintinib or placebo: interruption or discontinuation of therapy and 2 sequential dose reductions to 4 mg and 3 mg (once daily) allowed in case of toxicity	
	Pretreatment **Required** ▪ fluoropyrimidine-, oxaliplatin-[c], and irinotecan-based chemotherapies ▪ anti-VEGF therapy ▪ for RAS wild type: anti-EGFR therapies ▪ for MSI-H or dMMR: checkpoint inhibitors, and for BRAF mutation: BRAF inhibitor, taking into account country-specific approval and availability, unless these are unsuitable for the patients ▪ trifluridine/tipiracil or regorafenib[d] **Disallowed** ▪ ≤ 60 days prior to the first dose of study drug: brachytherapy, surgery or invasive procedure[e] (e.g. biopsy and central venous catheter placement) ▪ ≤ 4 weeks prior to the first dose of study drug: live vaccines, systemic antineoplastic therapies[f] or investigational products (including chemotherapy, radical radiotherapy, hormonal therapy, biotherapy and immunotherapy) ▪ ≤ 4 weeks or 5 half-lives (whichever is shorter) prior to the first dose of study drug: systemic small molecule targeted therapies (e.g. tyrosine kinase inhibitors) ▪ ≤ 2 weeks prior to the initiation of study drug: palliative radiotherapy for bone metastases/lesions **Concomitant treatment** **Allowed** ▪ for prophylaxis: anticoagulants and anti-emetics ▪ granulocyte colony-stimulating factors, granulocyte macrophage colony-stimulating factors, platelet simulating factors or erythropoietin ▪ palliative radiation[g] for symptom control **Disallowed** ▪ any other antineoplastic therapy, including chemotherapy, hormonal therapy, biologic therapy, radiotherapy, or herbal therapy	

Table 7: Characteristics of the intervention – fruquintinib + BSC vs. placebo + BSC (multipage table)

Study	Intervention	Comparison
a. Module 4 A of the dossier does not contain any specific information on the measures included in BSC. According to the study documents, all supportive measures consistent with optimal patient care were to be given throughout the study. A specification results from the allowed/disallowed concomitant treatment. b. Treatment could be suspended for up to 14 days during the study. If a treatment interruption of more than 14 days was necessary, treatment was to be discontinued. Once a dose had been reduced, it could not be re-escalated. c. Adjuvant therapy with oxaliplatin in the non-metastatic stage of disease was acceptable if patients developed metastatic disease during or within 6 months of completing therapy; if this was not the case, pretreatment had to be in the metastatic setting. d. Progression under or intolerance to trifluridine/tipiracil or regorafenib was an inclusion criterion for the study. Patients were considered intolerant if they have received at least one dose of either drug and were discontinued from therapy for reasons other than disease progression. Prior treatment with both therapies (both trifluridine/tipiracil and regorafenib) was permitted. e. Or unhealed surgical incision. f. With the exception of brachytherapy. g. Provided it does not compromise tumour assessments of target lesions. Study treatment had to be suspended during the radiation period and not resumed until at least 7 days after radiation only after meeting the following criteria: radiation-related toxicities resolved to grade ≤ 2, and no disease progression. ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; dMMR: mismatch repair deficiency; EGFR: epidermal growth factor receptor; MSI-H: high-frequency microsatellite instability; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor		

Study design

The FRESCO-2 study is a multinational, double-blind RCT comparing fruquintinib + BSC versus placebo + BSC. Patients were included if they were at least 18 years old (in Japan at least 20 years old) and had histologically or cytologically documented metastatic colorectal adenocarcinoma. At study start, patients had to be in good general condition according to an ECOG PS of 0 or 1, and have an expected survival time of > 12 weeks. RAS and BRAF mutation status as well as microsatellite instability/mismatch repair status had to be documented.

According to the inclusion criteria, patients must have been previously treated with all standard therapies for the metastatic stage of the disease and must have progressed on or been intolerant to treatment with either trifluridine/tipiracil or regorafenib. Standard treatment regimens had to include the following drugs: fluoropyrimidine, oxaliplatin and irinotecan, and an anti-VEGF biological therapy (e.g. bevacizumab, aflibercept, ramucirumab), and, if rat sarcoma viral oncogene homologue (RAS) wild type, an anti-EGFR therapy (e.g. cetuximab or panitumumab). Adjuvant chemotherapy with oxaliplatin in the non-metastatic setting was acceptable if patients relapsed during or within 6 months of completing adjuvant chemotherapy. If this was not the case, pretreatment with oxaliplatin had to be in the

metastatic setting. In addition, patients with MSI-H or dMMR tumours had to be pretreated with immune checkpoint inhibitors, and patients with BRAF mutation had to be pretreated with a BRAF inhibitor unless these were unsuitable for the patients.

A total of 691 patients were included and randomly assigned in a ratio of 2:1, either to treatment with fruquintinib + BSC (461 patients) or to treatment with placebo + BSC (230 patients). Stratification factors were RAS mutation status (wild type versus mutant), the time since diagnosis of first metastasis (≤ 18 months versus > 18 months), and prior therapy with trifluridine/tipiracil versus regorafenib versus both trifluridine/tipiracil and regorafenib.

Treatment with fruquintinib was largely in compliance with the specifications of the SPC [8]. Patients in the intervention arm received 5 mg of fruquintinib once daily for 21 consecutive days of the 28-day treatment cycles. Patients in the comparator arm received matching placebo capsules according to the same administration schedule. All patients additionally received concomitant treatment, which could include, but was not limited to, haematological supportive therapies, anti-emetics, and palliative radiation for symptom control. However, any other antineoplastic therapies, including chemotherapy, were not permitted as concomitant treatment. Study treatment was administered until disease progression or occurrence of unacceptable toxicity.

Treatment switching from the comparator to the intervention arm was not planned according to the planning of the study. About 30% of the patients received subsequent therapy after completion of the randomized study treatment (see Table 11).

The primary outcome was overall survival. Patient-relevant outcomes of morbidity, health-related quality of life and side effects were additionally recorded.

According to Module 4 A in the company’s dossier, the study was terminated because the planned number of 480 events in the outcome of overall survival for the final analysis had been exceeded (490 deaths). According to information in the study documents, however, patients who were still on study treatment at the time of study completion could continue to receive study treatment if they were experiencing clinical benefit and no undue risks. According to information in the study documents, 20 patients in the intervention arm and one patient in the comparator arm were still receiving study treatment at the final data cut-off date.

For the FRESCO-2 study, the company presented results on the final data cut-off of 24 June 2022 in the dossier. The present benefit assessment uses the results from this data cut-off for the derivation of the added benefit.

The FRESCO-2 study has several uncertainties that are relevant for the present benefit assessment. In particular, this concerns a high number of major protocol violations that

occurred during the conduct of the study, the necessary prior therapies in the population of the present research question and the implementation of the ACT. These topics are discussed in detail below.

Limitations of the FRESCO-2 study

Study conduct (protocol violations)

Study documents show that 613 (89%) of the patients included in the study had at least one major protocol deviation in the course of the study. The total number of patients with at least one protocol deviation classified as major according to the information in the study documents is slightly higher in the intervention arm (90%) than in the comparator arm (85%) (see Table 19 in I Appendix B of the full dossier assessment). The most frequent major protocol deviations during the course of the study concerned missed study procedures (53% of patients in the intervention arm versus 44% in the comparator arm), the dosage of the study medication (51% versus 40%), and the inclusion and exclusion criteria (36% versus 35%).

In the dossier's Module 4 D, the company presented no information on protocol deviations. Based on the available information in Module 5 of the dossier, it remains unclear to what extent the planning of the study was deviated from in detail and how the deviations affected the treatment in the study or the recording of patient-relevant outcomes. The study documents only contain a general statement that there were no effects on safety and efficacy despite the large number of major protocol deviations. Although the documents contain sensitivity analyses based on a per-protocol population, these analyses excluded only 17 patients in the intervention arm and 5 in the comparator arm compared with the analyses based on the intention-to-treat population. It remains unclear why only this small number of patients was excluded, although important protocol violations occurred in notably more patients. Furthermore, the study documents do not contain any information on how a major protocol violation was defined. Although it can be inferred from the available information that the study was conducted during the COVID-19 pandemic, the documentation does not show that the conditions during the pandemic actually led to the high number of deviations. Although a corresponding field for deviations due to the pandemic was provided in the electronic data capture system, this was only completed in a few cases (for a total of 12 patients in both study arms). According to the clinical study report (CSR), the documented deviations probably were an underestimation of the deviations caused by the pandemic. Although this seems plausible in view of the period in which the study was conducted, it ultimately remains unclear on the basis of the study documentation. In addition, it cannot generally be assumed that the deviations caused by the COVID-19 pandemic affected all patient groups or both study arms equally. The available data show differences in the proportion of patients between the study arms, particularly with regard to the major protocol deviations concerning the dosage of the study medication and the missed study procedures. Overall, it remains unclear whether the major protocol deviations influenced the available

analyses of the FRESCO-2 study. This uncertainty has been taken into account in the assessment of the risk of bias of results (see Section I 4.2).

Suitability of the study population for the present benefit assessment

In the present therapeutic indication, patients must have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. Patients must also have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib. According to the G-BA's specification of the ACT, it is also assumed that patients with BRAF V600E mutation were treated with a BRAF inhibitor and patients with MSI-H or dMMR were treated with a checkpoint inhibitor. It is also assumed that the patients received all the therapies mentioned or were not eligible for them. However, according to the G-BA, regorafenib is no longer on the market in Germany at the time of this benefit assessment. The company also described in Module 3 A of the dossier that the drug has no longer been available in Germany since 2016 and is therefore of no great importance in clinical practice. Regarding the importance in clinical practice, the company referred to a study based on the database of the Institute for Applied Health Research Berlin (InGef) [9] on treatment of colorectal cancer with trifluridine/tipiracil, which shows that regorafenib was not prescribed or administered both in the treatment line before and in the treatment line after administration of trifluridine/tipiracil in the years from 2017 to 2021. In contrast to pretreatment with trifluridine/tipiracil, pretreatment with regorafenib therefore does not correspond to the German health care context.

According to the company, the majority of patients in the FRESCO-2 study were recruited in European centres, but only 19 of these patients were recruited in Germany. Correspondingly, a large proportion (48%) of patients had also been pretreated with regorafenib, including 8% of patients pretreated exclusively with regorafenib and not with trifluridine/tipiracil. Nevertheless, the majority of patients had been pretreated with trifluridine/tipiracil. Although the proportion of patients who did not receive trifluridine/tipiracil is low, it remains unclear whether these patients could still have benefited from treatment with trifluridine/tipiracil.

With regard to the other prior therapies specified according to the therapeutic indication, it can be inferred from the available information on protocol violations that patients were also included in the study without fulfilling the inclusion criterion of pretreatment with anti-VEGF therapies before the start of the study. However, at around 96%, the majority of the study population received a corresponding pretreatment. The other required prior therapies according to the present research question were also administered to the majority of patients (see Table 9), in the case of EGFR, immune checkpoint and BRAF inhibitors in relation to the respective population for which these therapies are indicated (RAS wild type, MSI-H and/or dMMR, BRAF mutation).

Overall, it remains unclear whether the results of the FRESCO-2 study are fully transferable to patients in the German health care context due to the limitations in prior therapy described above. This uncertainty is taken into account when assessing the certainty of conclusions (see Section I 4.2).

Implementation of the appropriate comparator therapy and administration of subsequent therapies

As described in the section on study design, patients in the FRESCO-2 study received supportive concomitant treatment, which could include, but was not limited to, haematological supportive therapies, anti-emetics, and palliative radiation for symptom control provided this did not compromise tumour assessments of target lesions. However, any other antineoplastic therapies, including chemotherapy, were not permitted as concomitant treatment. This contradicts the guideline on palliative care [10], which emphasizes that the management and the alleviation of distressing symptoms are a key part of palliative care when treating patients with incurable cancer. Symptom-oriented measures can be implemented on their own or parallel to tumour-related or causal therapies. According to the guideline, an either-or is not appropriate, which is why tumour-specific measures (e.g. radiotherapy, surgical procedures, antitumour drug treatments) should be weighed up against the primary or sole therapeutic goal of symptom relief. The exclusion of further antineoplastic therapies including chemotherapy in the study therefore potentially means a restriction of palliative therapy. Data on subsequent therapies also show that a relevant proportion of patients in both the intervention arm (29%) and the comparator arm (34%) received at least one further subsequent antineoplastic therapy after completion of study medication (see Table 11), including chemotherapy. With a proportion of 95% or 99% of patients who discontinued treatment (see Table 9), around 1 third of patients who discontinued treatment thus received subsequent treatment(s). This high proportion shows that there was a need for further treatment also with systemic therapies after the end of the randomized study medication. It remains unclear whether the administration of additional treatment options in the comparator arm of the study might have been indicated already during the randomized study treatment. Against this background, there is overall uncertainty as to whether BSC was fully implemented in the FRESCO-2 study or whether there was potentially undertreatment in some of the patients. This uncertainty is taken into account when assessing the certainty of conclusions (see Section I 4.2).

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC

Study **Outcome category** **Outcome**	**Planned follow-up observation**
FRESCO-2	
Mortality	
Overall survival	Until death or withdrawal of consent[a]
Morbidity	
Health status (EQ-5D VAS)	Until 7 days after treatment end
Symptoms (EORTC QLQ-C30)	Until 7 days after treatment end
Health-related quality of life	
EORTC QLQ-C30	Until 7 days after treatment end
Side effects	
All outcomes in the side effects category	Until 37[b] days after the last dose of the study medication or until initiation of a new antineoplastic treatment, whichever was first

a. Patients who withdrew their informed consent to the study could be followed up for survival unless they explicitly declined further follow-up observation after withdrawing consent.
b. Discrepancies between statistical analysis plan (37 days) and study protocol (30 days); AE analyses in Module 4 A refer to 37 days.

AE: adverse event; BSC: best supportive care; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

The observation periods for the outcomes on morbidity, health-related quality of life, and side effects were systematically shortened because they were recorded only for the period of treatment with the study medication (plus 7 or 37 days respectively). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC (multipage table)

Study **Characteristic** **Category**	**Fruquintinib + BSC** **N = 461**	**Placebo + BSC** **N = 230**
FRESCO-2		
Age [years], mean (SD)	62 (10)	62 (10)
Sex [F/M], %	47/53	39/61
Family origin, n (%)		
Asian	43 (9)	18 (8)
Caucasian	367 (80)	192 (83)
Black/African American	13 (3)	7 (3)
Other/unknown	38 (8)	13 (6)
Geographical region, n (%)		
Asia-Pacific	50 (11)	22 (10)
Europe	329 (71)	166 (72)
North America	82 (18)	42 (18)
ECOG Performance Status, n (%)		
0	196 (43)	102 (44)
1	265 (57)	128 (56)
Disease duration: time between first diagnosis and randomization [months], median [Q1; Q3]	47.2 [30.6; 67.4]	49.4 [33.4; 74.8]
Duration of metastatic disease [months], median [Q1; Q3]	37.9 [26.1; 56.8]	41.0 [28.0; 59.9]
Location of primary tumour at first diagnosis, n (%)		
Colon	279 (61)	137 (60)
Rectum	143 (31)	70 (30)
Colon and rectum	39 (8)	23 (10)
RAS status, n (%)		
Wild type	170 (37)	85 (37)
Mutant	291 (63)	145 (63)
BRAF status, n (%)		
Wild type	401 (87)	198 (86)
BRAF V600E mutation	7 (2)	10 (4)
Other	53 (11)	22 (10)
Microsatellite/mismatch repair status, n (%)		
MSS and/or pMMR	427 (93)	215 (93)
MSI-H and/or dMMR	5 (1)	4 (2)
Unknown	29 (6)	11 (5)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC (multipage table)

Study **Characteristic** **Category**	**Fruquintinib + BSC** **N = 461**	**Placebo + BSC** **N = 230**
Number of metastasized organs other than colon or rectum, n (%)		
0	0 (0)	1 (< 1)
1	61 (13)	44 (19)
> 1	400 (87)	185 (80)
Number of prior treatment lines, median [Q1; Q3]	5.0 [4.0; 6.0]	5.0 [4.0; 6.0]
Number of prior treatment lines for metastatic disease, n (%)		
≤ 3	125 (27)	64 (28)
> 3	336 (73)	166 (72)
Prior anticancer therapy with fluoropyrimidine, oxaliplatin and irinotecan, n (%)		
Fluoropyrimidine	460 (> 99)	230 (100)
Oxaliplatin	460 (> 99)	228 (> 99)
Irinotecan	459 (> 99)	229 (> 99)
Prior treatment with VEGF inhibitors, n (%)		
Yes	445 (97)	221 (96)
No	16 (3)	9 (4)
Prior treatment with EGFR inhibitors, n (%)		
Yes	180 (39)	88 (38)
No	281 (61)	142 (62)
Prior treatment with an immune checkpoint inhibitor, n (%)		
Yes	21 (5)	11 (5)
No	440 (95)	219 (95)
Prior treatment with a BRAF inhibitor, n (%)		
Yes	9 (2)	7 (3)
No	452 (98)	223 (97)
Prior treatment with trifluridine/tipiracil and/or regorafenib, n (%)		
Trifluridine/tipiracil	240 (52)	121 (53)
Regorafenib	40 (9)	18 (8)
Trifluridine/tipiracil or regorafenib	181 (39)	91 (40)
Treatment discontinuation, n (%)[a]	438 (95[b])	227 (99[b])
Study discontinuation, n (%)[c]	337 (73[b])	184 (80[b])

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC (multipage table)

Study Characteristic Category	Fruquintinib + BSC N = 461	Placebo + BSC N = 230
a. Common reasons for treatment discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients; Institute's calculation): radiographic progression (59% vs. 64%), AE (20% vs. 17%), investigator decision (7% vs. 8%). An additional < 1% vs. < 1% of randomized patients never started treatment. b. Institute's calculation. c. Common reasons for study discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients; Institute's calculation): withdrawal of consent (3% vs. 3%) and other reasons (1% vs. 1%). The data additionally include patients who died during the course of the study (intervention arm: 69% vs. control arm: 75%). AE: adverse event; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; dMMR: mismatch repair deficiency; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; F: female; M: male; MSI-H: high-frequency microsatellite instability; MSS: microsatellite stable; n: number of patients in the category; N: number of randomized patients; pMMR: proficient mismatch repair; Q1: 1st quartile; Q3: 3rd quartile; RAS: rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; SD: standard deviation; VEGF: vascular endothelial growth factor		

Patient characteristics are largely balanced between the 2 treatment arms. The mean patient age was 62 years, and most patients were from Europe, but only 19 patients were recruited in Germany, according to the company. There were minor differences in the proportion of women, which was slightly higher in the intervention arm (47%) than in the comparator arm (39%).

The included patients were in good general condition at the start of the study, with 57% having an ECOG PS of 1. Patients with ECOG PS ≥ 2 were not included in the FRESCO-2 study. However, a non-interventional study on treatment with trifluridine/tipiracil in clinical practice in Germany, which the company also referred to in Module 4 A of the dossier, showed that around 17% of patients treated with this therapy in German clinical practice have an ECOG PS > 1 [11]. The assessment report of the European Medicines Agency also states that 10 to 17% of patients treated in various late lines have ECOG ≥ 2, and that the results based on the study population restricted to ECOG PS ≤ 1 may not reflect use in the late line of therapy in clinical practice [12]. Based on the FRESCO-2 study, conclusions can therefore only be derived for patients with an ECOG PS ≤ 1. It remains unclear whether the effects observed in the study are transferable to patients with an ECOG PS ≥ 2. Around 37% of patients had RAS wild type, and only very few patients had a BRAF mutation (2% versus 4%) or MSI-H and/or dMMR (1% versus 2%). Accordingly, around 39% of patients had been pretreated with EGFR inhibitors, and a small proportion of patients with BRAF or immune checkpoint inhibitors. Even though, according to the inclusion criteria, all patients should have already received treatment

with VEGF inhibitors, 3% in the intervention arm and 4% in the comparator arm had not been pretreated accordingly. Although, contrary to the procedure in German clinical practice, 8% of patients had been pretreated exclusively with regorafenib and not with trifluridine/tipiracil, and 39% with both regorafenib and trifluridine/tipiracil, the majority of patients had been pretreated with trifluridine/tipiracil. Although the proportion of patients who did not receive trifluridine/tipiracil is low, it remains unclear whether these patients could still have benefited from treatment with trifluridine/tipiracil. With the exception of individual patients, all other prior therapies were administered in accordance with the present research question. Overall, more than 72% of patients in the study had been pretreated with more than 3 systemic therapies in the metastatic setting. For a detailed discussion of the pretreatment of the patients included in the study and the consequences for the benefit assessment, see the text section *Suitability of the study population for the present benefit assessment*.

Although, according to the SPC, treatment with fruquintinib is an option for all tumour types of metastatic colorectal cancer [8], the FRESCO-2 study included only patients with adenocarcinoma. However, this tumour type accounts for the majority of adenocarcinomas (over 95%) [13,14].

At the data cut-off, 95% of patients in the intervention arm and 99% of patients in the comparator arm had discontinued therapy. The most common reasons were radiographic progression (59% versus 64%) or AEs (20% versus 17%). The study was discontinued by 73% versus 80% of patients. This was mainly due to deaths (69% versus 75%). In addition, around 3% of patients withdrew consent.

Treatment duration and observation period

Table 10 shows the mean and median treatment duration of the patients and (if available) the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC

Study **Duration of the study phase** **Outcome category/outcome**	**Fruquintinib + BSC** **N = 461**	**Placebo + BSC** **N = 230**
FRESCO-2		
Treatment duration [months]		
Median [Q1; Q3]	3.1 [1.8; 5.6][a]	1.8 [1.0; 2.3]
Mean (SD)	4.0 (3.1)[a]	2.0 (1.4)
Observation period [months]		
Overall survival[b]		
Median [Q1; Q3]	11.3 [9.0; 14.2]	11.2 [8.7; 15.5]
Mean (SD)	ND	ND
Morbidity		
Health status (EQ-5D VAS)[c]		
Median [min; max]	2.8 [0.0; 18.9]	1.9 [0.0; 11.6]
Mean (SD)	3.9 (3.1)	1.8 (1.5)
Symptoms (EORTC QLQ-C30)[c]		
Median [min; max]	2.8 [0.0; 18.9]	1.9 [0.0; 11.6]
Mean (SD)	3.8 (3.1)	1.8 (1.5)
Health-related quality of life (EORTC QLQ-C30)[c]		
Median [min; max]	2.8 [0.0; 18.9]	1.9 [0.0; 11.6]
Mean (SD)	3.8 (3.1)	1.8 (1.5)
Side effects[d]		
Median [min; max]	3.9 [0.6; 20.1][a]	2.8 [0.2; 13.0]
Mean (SD)	5.0 (3.2)[a]	2.9 (1.5)

a. Number of analysed patients: N = 456.
b. Calculated using the reverse Kaplan-Meier method. According to the company, the observation period is defined as the time from the date of randomization to the date at which the patient was last known alive. Patients who were reported as deceased were censored at the date of death.
c. Calculated as (time point of last measurement – time point of randomization +1)/30.4375.
d. Calculated as (37 days after receiving the last dose of study drug – time of first dose of study drug)/30.4375.

BSC: best supportive care; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of randomized patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment duration was notably longer in the intervention arm than in the comparator arm (3.1 months for fruquintinib + BSC versus 1.8 months for placebo + BSC).

The median observation period for overall survival was about 11 months in both treatment arms. For the outcomes on morbidity, health-related quality of life, and side effects, the

observation periods were linked to the end of treatment and were therefore notably shorter in the comparator arm than in the intervention arm. In addition, the observation periods for these outcomes were therefore substantially shortened in comparison with the median observation period for overall survival. For the outcomes in the categories of morbidity and health-related quality of life, follow-up observation was planned up to 7 days after the end of treatment; for outcomes in the category of side effects, follow-up observation was planned up to 37 days after the end of treatment or the start of a new antineoplastic therapy (see Table 8). For these outcomes, conclusions can therefore be drawn only for the period up to 7 or 37 days after the end of treatment.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent therapies[a] – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC (FRESCO-2 study)

Study **Drug class[b]** **Drug**	**Patients with subsequent therapy, n (%)**	
	Intervention **N = 456[c]**	**Comparison** **N = 230[c]**
FRESCO-2		
Total	134 (29.4)	79 (34.3)
Antineoplastic drugs	132 (28.9)	78 (33.9)
5-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)
Capecitabine	25 (5.5)	10 (4.3)
Irinotecan	22 (4.8)	10 (4.3)
Tipiracil hydrochloride/trifluridine	10 (2.2)	4 (1.7)
Cetuximab	9 (2.0)	4 (1.7)
Panitumumab	8 (1.8)	4 (1.7)
5-fluorouracil/folinic acid + oxaliplatin	3 (0.7)	5 (2.2)
Investigational antineoplastic drug	5 (1.1)	2 (0.9)
Irinotecan hydrochloride	4 (0.9)	2 (0.9)
Tipiracil/trifluridine	4 (0.9)	2 (0.9)
Calcium folinate + 5-fluorouracil + irinotecan hydrochloride	3 (0.7)	2 (0.9)
Raltitrexed	2 (0.4)	3 (1.3)
All other therapeutic agents	30 (6.6)	18 (7.8)
Folinic acid	18 (3.9)	12 (5.2)
Calcium folinate	7 (1.5)	5 (2.2)
Calcium levofolinate	5 (1.1)	1 (0.4)

a. Subsequent therapies used in at least 3 patients in at least one study arm.
b. ATC subgroup.
c. Patients who received at least one dose of the study medication.

ATC: Anatomical Therapeutic Chemical; BSC: best supportive care; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

The FRESCO-2 study implemented no restrictions regarding the administration of subsequent therapies. The proportion of the drugs used as subsequent therapy were largely balanced between the treatment arms. Overall, 28.9% of the patients in the intervention arm and 33.9% of the patients in the comparator arm received subsequent antineoplastic therapy. The most frequently used drugs were 5-fluorouracil (7.7% versus 9.6%), regorafenib (7.5% versus 7.8%) and oxaliplatin (6.4% versus 6.5%). In addition, 5.5% of the patients in the intervention arm

and 9.6% of the patients in the comparator arm received radiotherapy. Overall, 95% of the patients in the intervention arm and 99% of the patients in the comparator arm discontinued treatment (see Table 9). Approximately one third of these patients received subsequent antineoplastic therapy, mostly with the drugs that are part of the necessary prior therapies in the present therapeutic indication. According to the S3 guideline on colorectal cancer, re-induction of antineoplastic substances that have been shown to be effective in early lines of therapy is an established therapeutic strategy in oncology, but evidence for the clinical effectiveness of this approach is limited [15]. According to the guideline, no other drugs are available in the framework of the approval that can be considered after undergoing the standard therapies. However, as already described in the section on the implementation of the ACT and administration of subsequent therapies, the proportion of patients with subsequent treatment(s) shows that there was a need for further treatment, including systemic therapies, after the end of the randomized study medication. It remains unclear whether the administration of additional treatment options, possibly also in the form of a re-induction of already administered antineoplastic agents, might have been indicated in the comparator arm of the study already during the randomized study treatment. As described above, this uncertainty is taken into account when assessing the certainty of conclusions (see Section I 4.2).

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
FRESCO-2	Yes	Yes	Yes	Yes	Yes	No[a]	High

a. In the course of the study, a high proportion of patients had ≥ 1 major protocol violation, which partly differed between the study arms (see Table 19 in I Appendix B of the full dossier assessment). Since it remains unclear to what extent the planning of the study was deviated from and how the deviations affected the analyses of the FRESCO-2 study, there is a high risk of bias at study level.

BSC: best supportive care; RCT: randomized controlled trial

The risk of bias across outcomes is rated as high for the FRESCO-2 study. This is due to the great number of protocol violations in the study, for which it remains unclear to what extent the planning of the study was deviated from and how the deviations affected treatment in the

study or the recording of patient-relevant outcomes and thus the available analyses of the FRESCO-2 study (for a detailed explanation, see text section on the conduct of the study [protocol violations] in this section).

Transferability of the study results to the German health care context

The company described that a total of 691 patients from 14 countries participated in the pivotal FRESCO-2 study for European approval, with the vast majority (71.6%) of patients being recruited in European centres, including 19 patients in Germany. It also described that the treatment regimen was in compliance with the specifications in the SPC and corresponded to everyday practice in Germany.

In addition, the company stated that the median age of the study population was representative of patients with refractory metastatic colorectal cancer in German clinical practice. In Module 4 A of the dossier, the company referred to the median age of 64 years of the patients included in the study, stating that this corresponded to the median age of patients treated with trifluridine/tipiracil in the German health care context. In this regard, it referred to the InGef investigation on treatment with trifluridine/tipiracil [9] mentioned in the section *Suitability of the study population for the present benefit assessment* and to a non-interventional study on treatment with trifluridine/tipiracil in health care in Germany [11]. The median patient age in these studies was around 63-67 and 68 years respectively.

According to the company's assessment, the fact that most patients in the FRESCO-2 study were male and the majority had an ECOG PS of 1 was also representative of the German health care context. Furthermore, the company described that in most cases the primary tumour was located in the left colon and many patients had liver metastases at the start of the study, that more than one in 3 patients had RAS wild type, whereas only a few patients had a BRAF V600E mutation or a microsatellite unstable tumour.

Furthermore, the company also discussed the pretreatment of the study participants in comparison with pretreatment in the German health care context.

According to the company, it can be concluded overall that the FRESCO-2 study is a very good reflection of the treatment situation in Germany in terms of treatment, patient characteristics and previous therapies. According to the company, unrestricted transferability of the study results to the German health care context can therefore be presumed.

For further details on the transferability of the study results with regard to the aspects described above, see also the text section *Suitability of the study population for the present benefit assessment* and the text section *Characteristics of the study population*. The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - health status, recorded with the EQ-5D VAS
  - symptoms, recorded with the EORTC QLQ-C30
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - gastrointestinal perforation (SMQ, AEs)
  - diarrhoea (PT, AEs)
  - hand-foot syndrome (PT, severe AEs)
  - haemorrhages (SMQ, AEs, severe AEs)
  - hypertension (SMQ, severe AEs)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows the outcomes for which data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC

Study	Outcomes												
	Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Gastrointestinal perforation (SMQ, AEs)	Diarrhoea (PT, AEs)	Hand-foot syndrome[b] (PT, severe AEs[a])	Haemorrhages (SMQ, AEs, severe AEs[a])	Hypertension (SMQ, severe AEs[a])	Other specific AEs[c]
FRESCO-2	Yes	No[d]	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized via severe AEs (CTCAE grade ≥ 3) of the PT palmar-plantar erythrodysaesthesia syndrome coded according to MedDRA.
c. The following events are considered (coded according to MedDRA): mucosal inflammation (PT, AEs), stomatitis (PT, AEs), dysphonia (PT, AEs), and abnormal hepatic function (operationalized via the SMQ "Drug related hepatic disorders – comprehensive search", SAEs).
d. No suitable data; for reasons, see the section following the table.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale

Health status, symptoms, and health-related quality of life

For the patient-reported outcomes (health status, recorded with the EQ-5D VAS; symptoms and health-related quality of life, each recorded with the EORTC QLQ-C30), the company presented both responder analyses, operationalized as time to first improvement/ deterioration, and continuous analyses. The outcomes were to be recorded at the beginning of each treatment cycle. In both treatment arms, however, the return rates of the questionnaires decreased markedly already early in the course of the study. Accordingly, the response rates in both treatment arms were already well below 70% from the 2nd recording after baseline, with notable differences between the treatment arms (response rates at the beginning of Cycle 3: 59.1% versus 30.2% for the EQ-5D VAS, and 58.7% versus 29.1% for the EORTC QLQ-C30). Consequently, the majority of patients had only one subsequent recording after the start of the study in Cycle 2; and even at this time point, response rates were already decreasing and differed between the study arms (response rates at the start of Cycle 2: 82.3% versus 77.4% for the EQ 5D-VAS, and 81.0% versus 76.9% for the EORTC QLQ-C30). The

percentages refer to patients who had not died at the respective time points of recording. Due to the small proportion of patients for whom data were recorded, it is therefore not possible to draw any valid conclusions about the comparison within the scope of the study. The analyses of the patient-reported outcomes presented by the company are therefore unsuitable for the benefit assessment.

Overall, it should be noted that informative data on these outcomes are of particular importance in the present palliative situation, in which the symptoms and health-related quality of life of patients with an overall poor prognosis play a key role. To obtain these data, a recording – beyond the end of the short treatment period in the present situation – would be necessary.

Quality-adjusted time without symptoms or toxicity

In Module 4 A of the dossier, the company presented analyses of the outcome of quality-adjusted time without symptoms or toxicity (Q-TWiST). According to the company, this outcome describes the patients' survival time adjusted for quality of life, which is assessed on the basis of disease control and severe AEs. On the one hand, the outcome included data on the time without progression, which was recorded according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 on the basis of imaging techniques. On the other, it included data on the duration of overall survival and the time without occurrence of severe AEs according to CTCAE grade 3 or 4 (with lower weight attributed to the survival time after progression and the time from occurrence of severe AEs to progression).

For the representation of the time without symptoms, the outcome included data on progression based on the RECIST criteria version 1.1, which are based exclusively on imaging techniques and therefore do not have to be directly associated with symptoms perceived by patients. This means that the operationalization of the outcome also includes components that are not directly patient relevant and is not suitable for this reason alone. The Q-TWiST outcome was therefore excluded from the benefit assessment. In addition, analyses of overall survival and severe AEs are considered in the present assessment via the respective outcomes of overall survival and severe AEs.

Inadequate processing of data on frequent AEs

In the dossier's Module 4 D, the company presented information on AEs that was inadequately processed. According to the dossier template, in addition to the overall AE rates, results on all AEs (operationalized as MedDRA SOCs and PTs) are to be presented if they exceed a certain minimum frequency [16]. However, in Module 4 A of its dossier, the company only presented a subset of these AEs. AEs irrespective of severity that occurred in ≥ 10 patients in a study arm were presented. For severe AEs and SAEs, the company presented analyses of the threshold value ≥ 5% of patients in a study arm. According to the dossier template, however, all events

that occurred in ≥ 10 patients and in ≥ 1% of the patients in a study arm must also be reported, irrespective of severity [16].

In addition, the information on AEs, SAEs and severe AEs at SOC and PT level presented by the company in Module 4 A of the dossier with the (partly deviating) frequency threshold considered by the company is not complete when compared with the study documents in Module 5 of the dossier. For individual AEs, such as the PT fatigue (severe AEs) the and the PT diarrhoea (severe AEs), there is therefore only information on the frequencies based on the data from the CSR, but there are no time-to-event analyses. After comparison with the study documents, time-to-event analyses are nevertheless available in Module 4 A of the dossier for the majority of AEs that occurred with different frequencies between the study arms. Therefore, despite the inadequate processing by the company, it is not assumed that there are any consequences for the present benefit assessment in the present data situation.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC

Study	Study level	Outcomes												
		Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Gastrointestinal perforation (SMQ, AEs)	Diarrhoea (PT, AEs)	Hand-foot syndrome[b] (PT, severe AEs[a])	Haemorrhages (SMQ, AEs, severe AEs[a])	Hypertension (SMQ, severe AEs[a])	Other specific AEs[c]
FRESCO-2	H	H[d]	–[e]	–[e]	–[e]	H[d, f]	H[d, f]	H[d]	H[d, f]	H[d, f]	H[d, f]	H[d, f]	H[d, f]	H[d, f]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized via severe AEs (CTCAE grade ≥ 3) of the PT palmar-plantar erythrodysaesthesia syndrome coded according to MedDRA.
c. The following events are considered (coded according to MedDRA): mucosal inflammation (PT, AEs), stomatitis (PT, AEs), dysphonia (PT, AEs), and abnormal hepatic function (operationalized via the SMQ "Drug related hepatic disorders – comprehensive search", SAEs).
d. High risk of bias across outcomes.
e. No suitable data; see Section I 4.1 for reasons.
f. Incomplete observations for potentially informative reasons.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale

The risk of bias across outcomes for the FRESCO-2 study is high due to the great number of protocol violations in the study, for which it remains unclear to what extent the planning of the study was deviated from and how the deviations affected treatment in the study or the recording of patient-relevant outcomes and thus the available analyses (see Section I 3.2 for a detailed explanation). Correspondingly, this leads to a high risk of bias for the results of all individual outcomes surveyed in the study.

As described in Section I 3.2, there are additional differences in the duration of treatment and observation between the study arms. This results in uncertainty due to incomplete observations for potentially informative reasons, which also contribute to the high risk of bias of the results for the outcomes in the side effects category (except discontinuation due to AEs). The planned observation until the end of treatment (plus 37 days) for these outcomes

resulted in notable differences in median observation periods between the treatment groups (3.9 vs. 2.8 months). The observation period was thus determined by the reasons for treatment discontinuation (mainly by disease progression or AEs), with clear differences in the time points of occurrence of the events between the study arms.

No suitable data are available for other outcomes in the categories of morbidity and health-related quality of life because the proportions of missing values were too high (see Section I 4.1 for details). Hence, the risk of bias of the results is not assessed for these outcomes.

Summary assessment of the certainty of conclusions

It remains unclear whether the results of the FRESCO-2 study can be transferred without restriction to the target population in the German health care context. This is due to the fact that patients were included in the study who do not correspond to the population of the present research question with regard to prior therapy. Furthermore, it remains unclear whether BSC was fully implemented in the FRESCO-2 study (for a detailed discussion, see Section I 3.2). In addition, the risk of bias across outcomes for the FRESCO-2 study is deemed high due to a large number of protocol deviations because it remains unclear whether the deviations affected the results of the study (for a detailed discussion, see Section I 3.2). Overall, this reduces the certainty of conclusions of the study results for the present research question. Based on the FRESCO-2 study, at most hints, e.g. of an added benefit, can be derived for all presented outcomes.

I 4.3 Results

Table 15 summarizes the results of the comparison of fruquintinib + BSC with placebo + BSC in pretreated patients with metastatic colorectal cancer. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix C of the full dossier assessment, and the tables on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in I Appendix D of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC (multipage table)

Study Outcome category Outcome	Fruquintinib + BSC N	Fruquintinib + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Fruquintinib + BSC vs. placebo + BSC HR [95% CI]; p-value[a]
FRESCO-2					
Mortality					
Overall survival	461	7.4 [6.7; 8.2] 317 (68.8)	230	4.8 [4.0; 5.8] 173 (75.2)	0.66 [0.55; 0.80]< 0.001[b]
Morbidity					
Health status (EQ-5D VAS)	No suitable data[c]				
Symptoms (EORTC QLQ-C30)	No suitable data[c]				
Health-related quality of life					
EORTC QLQ-C30	No suitable data[c]				
Side effects					
AEs (supplementary information)[d]	456	0.3 [0.2; 0.3] 450 (98.7)	230	0.5 [0.4; 0.6] 211 (91.7)	–
SAEs[d]	456	11.0 [7.8; NC] 154 (33.8)	230	NA [5.4; NC] 72 (31.3)	0.77 [0.58; 1.03]; 0.102
Severe AEs[d, e]	456	2.9 [2.5; 3.7] 277 (60.7)	230	4.1 [3.4; 5.6] 103 (44.8)	1.20 [0.96; 1.51]; 0.078
Discontinuation due to AEs[d]	456	NA 85 (18.6)	230	NA 40 (17.4)	0.70 [0.47; 1.03]; 0.083
Gastrointestinal perforation (SMQ, AEs)	456	NA 16 (3.5)	230	NA 1 (0.4)	4.71 [0.61; 36.47]; 0.094
Diarrhoea (PT, AEs)	456	NA [10.9; NC] 110 (24.1)	230	NA 24 (10.4)	2.05 [1.31; 3.20]; 0.001
Hand-foot syndrome (PT, severe AEs)[f]	456	NA 29 (6.4)	230	NA 0 (0)	NC[g]; < 0.001
Haemorrhages (SMQ, AEs)	456	NA 65 (14.3)	230	NA [5.7; NC] 22 (9.6)	1.18 [0.72; 1.92]; 0.507
Haemorrhages (SMQ, severe AEs[e])	456	NA 8 (1.8)	230	NA 4 (1.7)	0.49 [0.14; 1.73]; 0.309
Hypertension (SMQ, severe AEs[e])	456	NA 64 (14.0)	230	NA 2 (0.9)	16.62 [4.07; 67.94]; < 0.001
Mucosal inflammation (PT, AEs)	456	NA [13.2; NC] 62 (13.6)	230	NA 6 (2.6)	4.91 [2.12; 11.38]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: fruquintinib + BSC vs. placebo + BSC (multipage table)

Study Outcome category Outcome	Fruquintinib + BSC N	Fruquintinib + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Fruquintinib + BSC vs. placebo + BSC HR [95% CI]; p-value[a]
Stomatitis (PT, AEs)	456	NA [18.0; NC] 67 (14.7)	230	NA 8 (3.5)	4.09 [1.96; 8.53]; < 0.001
Dysphonia (PT, AEs)	456	NA 74 (16.2)	230	NA 12 (5.2)	3.32 [1.80; 6.13]; < 0.001
Abnormal hepatic function (SMQ, SAEs)[h]	456	NA 11 (2.4)	230	NA 11 (4.8)	0.43 [0.18; 0.99]; 0.041

a. HR and CI: unstratified Cox regression model with the stratification factors and treatment group as covariates; p-value: stratified log-rank test. Stratification factors: prior therapy (trifluridine/tipiracil vs. regorafenib vs. trifluridine/tipiracil and regorafenib), RAS status (wild type vs. mutant), duration of metastatic disease (≤ 18 months vs. > 18 months).
b. HR and CI: stratified Cox regression model; p-value: stratified log-rank test. Stratification factors as in footnote a.
c. See Section I 4.1 of the present dossier assessment for the reasoning.
d. Without disease-related events (the PTs disease progression, malignant neoplastic progression, neoplastic progression, metastatic colorectal cancer, tumour pain, tumour invasion, metastasis, neoplastic meningitis, metastases to liver, CNS metastases, cancer pain, and metastatic lung cancer were not included).
e. Operationalized as CTCAE grade ≥ 3.
f. Operationalized via severe AEs (CTCAE grade ≥ 3) of the PT palmar-plantar erythrodysaesthesia syndrome coded according to MedDRA.
g. An effect estimate could not be calculated using the Cox regression model presented by the company. For severe AEs of the superordinate SOC skin and subcutaneous tissue disorders, which predominantly include the PT palmar-plantar erythrodysaesthesia syndrome, the following result is shown: 31 (6.8%) vs. 1 (0.4%); HR: 11.78 [1.60; 86.84]; p = 0.002.
h. Operationalized via SAEs of the SMQ “Drug related hepatic disorders – comprehensive search” coded according to MedDRA.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RAS: rat sarcoma viral oncogene homologue; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

Overall survival

A statistically significant difference in favour of fruquintinib + BSC in comparison with placebo + BSC was shown for the outcome of overall survival. There is a hint of an added benefit of fruquintinib in comparison with BSC.

Morbidity

Health status (EQ-5D VAS) and symptoms (EORTC QLQ-C30)

No suitable data are available for the outcomes of health status (recorded with the EQ-5D VAS) and symptoms (recorded with the EORTC QLQ-C30) (for reasoning, see Section I 4.1). There is no hint of an added benefit of fruquintinib in comparison with BSC; an added benefit is therefore not proven.

Health-related quality of life (recorded with the EORTC QLQ-C30)

No suitable data are available for the outcome of health-related quality of life (recorded using EORTC QLQ-C30) (for reasons, see Section I 4.1). There is no hint of an added benefit of fruquintinib in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from fruquintinib in comparison with BSC; greater or lesser harm is therefore not proven.

Specific AEs

Gastrointestinal perforation (SMQ, AEs) and haemorrhages (SMQ, AEs, severe AEs)

No statistically significant difference between treatment groups was shown for either of the outcomes of gastrointestinal perforation (SMQ, AEs) and haemorrhages (SMQ, AEs, severe AEs). In each case, there is no hint of greater or lesser harm from fruquintinib in comparison with BSC; greater or lesser harm is therefore not proven.

Diarrhoea (PT, AEs), hand-foot syndrome (PT, severe AEs), hypertension (SMQ, severe AEs), mucosal inflammation (PT, AEs), stomatitis (PT, AEs), and dysphonia (PT, AEs)

A statistically significant difference between treatment groups to the disadvantage of fruquintinib + BSC compared with placebo + BSC was shown for each of the outcomes of diarrhoea (PT, AEs), hand-foot syndrome (PT, severe AEs), hypertension (SMQ, severe AEs), mucosal inflammation (PT, AEs), stomatitis (PT, AEs), and dysphonia (PT, AEs). In each case, there is a hint of greater harm from fruquintinib in comparison with BSC.

Abnormal hepatic function (SMQ, SAEs)

A statistically significant difference between treatment groups in favour of fruquintinib + BSC in comparison with placebo + BSC was shown for the outcome of abnormal hepatic function (SMQ, SAEs). There is a hint of lesser harm from fruquintinib in comparison with BSC.

I 4.4 Subgroups and other effect modifiers

The following potential effect modifiers are taken into account in the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

In accordance with the described methods, no relevant effect modification by the characteristics of age or sex was identified for the outcomes for which suitable data are available.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 16).

Table 16: Extent of added benefit at outcome level: fruquintinib vs. BSC (multipage table)

Outcome category **Outcome**	**Fruquintinib + BSC vs. placebo + BSC** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	7.4 vs. 4.8 HR: 0.66 [0.55; 0.80]; p < 0.001 probability: "hint"	Outcome category: mortality CI_u < 0.85 added benefit, extent: "major"
Outcomes with shortened observation period		
Morbidity		
Health status (EQ-5D VAS)	No suitable data	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30)	No suitable data	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data	Lesser/added benefit not proven
Side effects		
SAEs	11.0 vs. NA HR: 0.77 [0.58; 1.03]; p = 0.102	Greater/lesser harm not proven
Severe AEs	2.9 vs. 4.1 HR: 1.20 [0.96; 1.51]; p = 0.078	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 0.70 [0.47; 1.03]; p = 0.083	Greater/lesser harm not proven
Gastrointestinal perforation (AEs)	NA vs. NA HR: 4.71 [0.61; 36.47]; p = 0.094	Greater/lesser harm not proven
Diarrhoea (AEs)	NA vs. NA HR: 2.05 [1.31; 3.20]; HR: 0.49 [0.31; 0.76][c]; p = 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Hand-foot syndrome (severe AEs)	NA vs. NA HR: NC[d]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"[d]
Haemorrhages (AEs)	NA vs. NA HR: 1.18 [0.72; 1.92]; p = 0.507	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: fruquintinib vs. BSC (multipage table)

Outcome category **Outcome**	**Fruquintinib + BSC vs. placebo + BSC** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Haemorrhages (severe AEs)	NA vs. NA HR: 0.49 [0.14; 1.73] p = 0.309	Greater/lesser harm not proven
Hypertension (severe AEs)	NA vs. NA HR: 16.62 [4.07; 67.94]; HR: 0.06 [0.01; 0.25][c]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Mucosal inflammation (AEs)	NA vs. NA HR: 4.91 [2.12; 11.38]; HR: 0.20 [0.09; 0.47][c]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Stomatitis (AEs)	NA vs. NA HR: 4.09 [1.96; 8.53]; HR: 0.24 [0.12; 0.51][c]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Dysphonia (AEs)	NA vs. NA HR: 3.32 [1.80; 6.13]; HR: 0.30 [0.16; 0.56][c]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Abnormal hepatic function (SAEs)	NA vs. NA HR: 0.43 [0.18; 0.99]; p = 0.041 probability: "hint"	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 lesser harm, extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. An effect estimate could not be calculated using the Cox regression model presented by the company. To derive the added benefit, the superordinate SOC skin and subcutaneous tissue disorders (severe AEs), whose events predominantly include the PT palmar-plantar erythrodysaesthesia syndrome, is therefore used instead: 31 (6.8%) vs. 1 (0.4%); HR: 11.78 [1.60; 86.84]; inverse direction of effect (Institute's calculation): 0.08 [0.01; 0.63]; p = 0.002.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of fruquintinib in comparison with BSC

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: hint of an added benefit – extent: "major"	–
Outcomes with shortened observation period	
Serious/severe side effects ▪ Abnormal hepatic function (SAEs): hint of lesser harm – extent: "minor"	Serious/severe side effects ▪ Hand-foot syndrome (severe AEs): hint of greater harm – extent "major" ▪ Hypertension (severe AEs): hint of greater harm – extent "major"
–	Non-serious/non-severe side effects ▪ Diarrhoea (AEs): hint of greater harm – extent: "considerable" ▪ Mucosal inflammation (AEs): hint of greater harm – extent: "considerable" ▪ Stomatitis (AEs): hint of greater harm – extent: "considerable" ▪ Dysphonia (AEs): hint of greater harm – extent: "considerable"
No suitable data are available for the outcomes of symptoms, health status and health-related quality of life.	
AE: adverse event; BSC: best supportive care; SAE: serious adverse event	

Overall, there is a hint of major added benefit for the outcome of overall survival. On the other hand, there are several negative effects for outcomes in the side effects category (in different severity categories), ranging from considerable to major extent. At the same time, no suitable data are available on the patient-reported outcomes of symptoms, health status and health-related quality of life. The negative effects and the missing data on the patient-reported outcomes do not completely challenge the positive effect for the outcome of overall survival, but influence the extent of the added benefit in the overall consideration.

In summary, there is a hint of considerable added benefit of fruquintinib in comparison with the ACT BSC for patients with metastatic colorectal cancer who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib.

Table 18 summarizes the result of the assessment of the added benefit of fruquintinib in comparison with the ACT.

Table 18: Fruquintinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Monotherapy for the treatment of adults with metastatic colorectal cancer ▪ who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and ▪ who have progressed on or are intolerant to treatment with either trifluridine/tipiracil or regorafenib[b, c]	BSC[d]	Hint of considerable added benefit[e]

a. Presented is the ACT specified by the G-BA.
b. Withdrawn from the German market.
c. The G-BA describes that, according to the inclusion criteria of the pivotal study for approval, patients must have already been pretreated with available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF therapies, and anti-EGFR therapies (for RAS wild type), as well as trifluridine/tipiracil and/or regorafenib. Furthermore, according to the G-BA it is assumed that patients with BRAF V600E mutation were treated with a BRAF inhibitor, and patients with high-frequency microsatellite instability (MSI-H) or with a mismatch repair deficiency (dMMR) were treated with a checkpoint inhibitor. According to the G-BA, it is assumed that the patients have received all the therapies mentioned or are not eligible for them.
d. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
e. The FRESCO-2 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; BSC: best supportive care; dMMR: mismatch repair deficiency; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; RAS: rat sarcoma viral oncogene homologue; VEGF: vascular endothelial growth factor

The assessment described above departs from that by the company, which derived an indication of considerable added benefit of fruquintinib in comparison with BSC based on the results of the FRESCO-2 study.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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